SOME REACTIONS OF STEROIDAL COMPOUNDS WITH SPECIAL REFERENCE TO CHOLESTANE SERIES

RESUME

THESIS SUBMITTED FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

IN

CHEMISTRY

TO THE

Aligarh Muslim University Aligarh

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Aligarh Muslim University Aligarh

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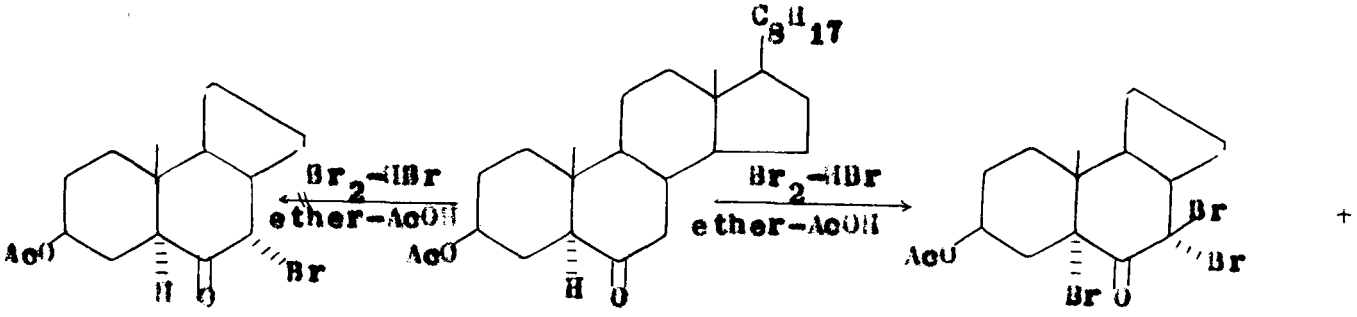
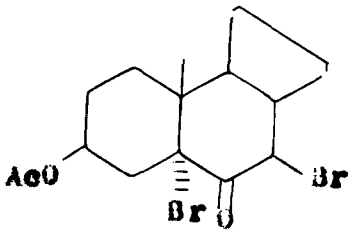
R E S U M E

PART - I (α-Bromination)

Previous work in these laboratories on α-bromination was concerned with an attempted preparation of 3β-acetoxy-7α-bromo-5α-cholestan-6-one (II) from 3β-acetoxy-5α-cholestan-6-one (I) which on treatment with Br_2-HBr in ether-acetic acid invariably afforded 3β-acetoxy-5,7,7-tribromo-5α-cholestan-6-one (III) and, in one or two experiment under similar conditions, 3β-acetoxy-5,7β-dibromo-5α-cholestan-6-one (IV). None of the products was found to be the desired 7α-bromoketone (II).

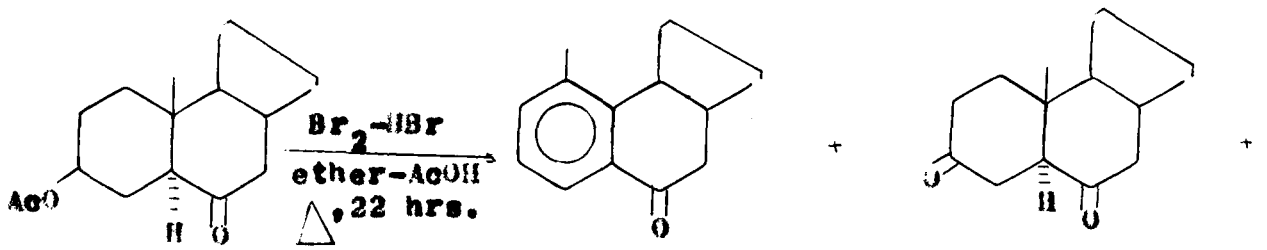


(II) (I) (III)

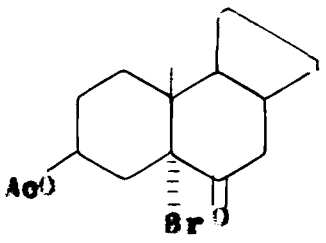


(IV)

In a continued effort to obtain (II), the ketone (I) was heated under reflux with Br_2 and HBr in ether-acetic acid which also failed to provide (II) but interestingly gave 1-methyl-19-norcholesta-1,3,5(10)-trien-6-one (V), a product of A-ring aromatization alongwith 5α-cholestane-3,6-dione (VI) and 3β-acetoxy-5-bromo-5α-cholestan-6-one (VII), which was shown to be an intermediate in the conversion of (I) into (V).

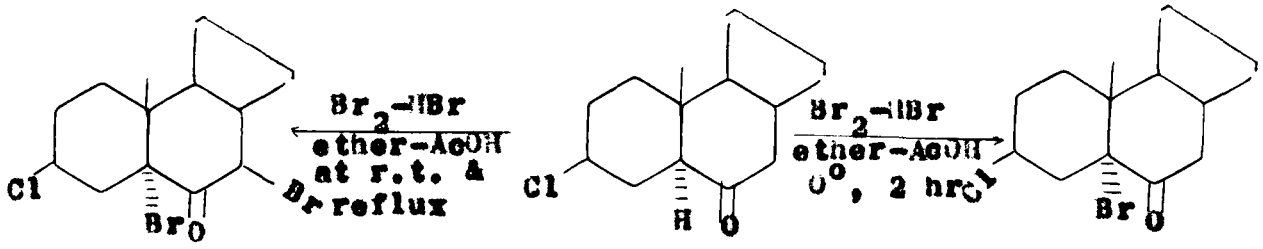


(I) (V) (VI)



(VII)

In continuation of the above work and in anticipation of obtaining some interesting results, 3β-chloro-5α-cholestan-6-one (VIII) was subjected to α-bromination under varying conditions. Reaction of (I) with bromine and HBr in ether-acetic acid in cold repeatedly gave 3β-chloro-5-bromo-5α-cholestan-6-one (IX). Bromination of the ketone (VIII) under essentially the same conditions of solvents and reagents but at room temperature and reflux temperature gave a different product of bromination, 3β-chloro-5,7β-dibromo-5α-cholestan-6-one (X). In no case we could obtain the product of ring A-aromatization of which we were desirous.

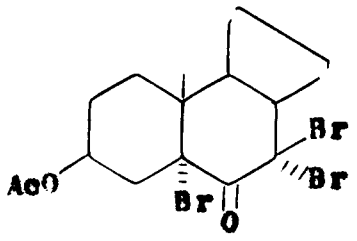


(X) (VIII) (IX)

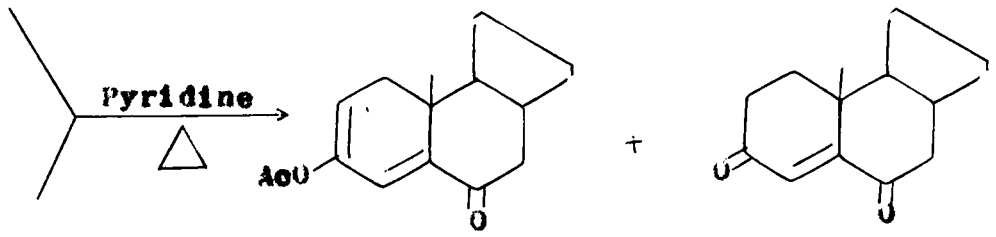
PART - II (Aromatisation via Dehydrohalogenation)

Concerning this subject it was previously noted that (III) and (IV) under reflux with pyridine provided 3-acetoxy-cholesta-2,4-dien-6-one (XI) and cholest-4-ene-3,6-dione (XII)

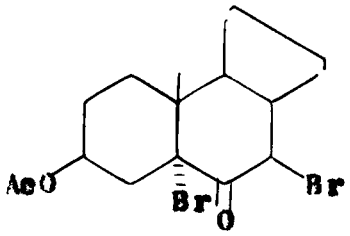
but none of the aromatised products which quite often result from pyridine-induced dehydrohalogenation of haloketosteroids.



(III)



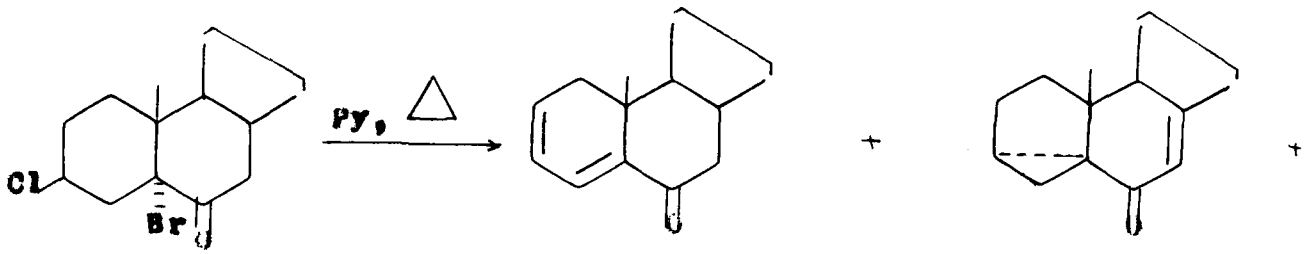
(XI) (XII)



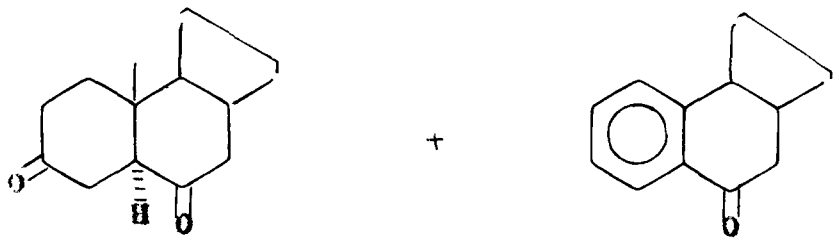
(IV)

Following these lines we also subjected 3β-chloro-5-bromo-5α-cholestan-6-one (IX) to dehydrohalogenation with pyridine under reflux. The aim of obtaining product of ring-A aromatization was successfully achieved in this reaction which provided cholesta-2,4-dien-6-one (XIII), 5α-cholestane-3,6-dione (VI),

3α,5-cyclo-5α-cholest-7-en-6-one (XIV) and the aromatized product, 19-norcholesta-1,3,5(10)-trien-6-one (XV). Structures have been established making use of their spectral properties, especially characteristic mass spectral fragmentation of each compound.



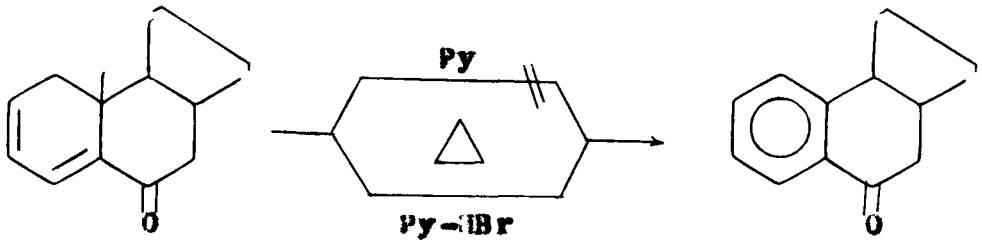
(IX) (XIII) (XIV)



(VI) (XV)

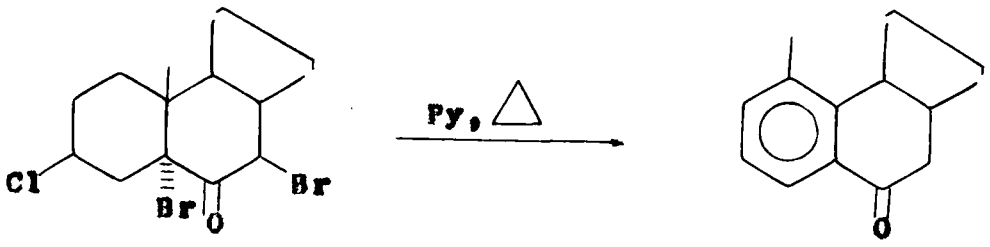
Mechanistic pathways have been suggested for the formation of the products (XIII), (VI), (XIV) and (XV) from (IX). The formation of the dienone (XIII) is a case of straightforward dehydrohalogenation of (IX). It has been suggested that traces

of water present in pyridine play a subtle role in the production of the dione (VI). The conversion of (IX) into (XIV) requires initial isomerisation of bromine from C5(α) to C7(α or β) and then dehydrohalogenation occurs during the course of the reaction. Regarding the aromatisation it has been shown by experiment that the dieneone (XIII) is the immediate precursor of the aromatised product (XV) since (XIII) under reflux with pyridine alone failed to give (XV) but in the additional presence of catalytic amounts of HBr (XIII) smoothly provided (XV), thereby supporting the proposed mechanism involving loss of C10-methyl group as methane.



(XIII) (XV)

When 3β-chloro-5,7β-dibromo-5α-cholestan-6-one (X) was refluxed with pyridine it furnished a product of ring A aromatization attended by methyl migration from C10 to C1, 1-methyl-19-norcholesta-1,3,5(10)-trien-6-one (XVI).

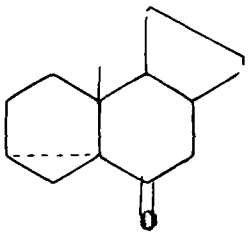


(X) (XVI)

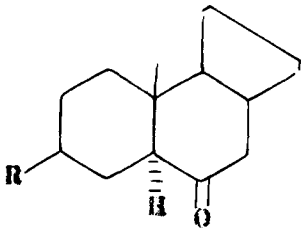
The mechanism proposed for this transformation finds analogy with those which have been established as a result of previous such studies.

PART - III (Azasteroids)

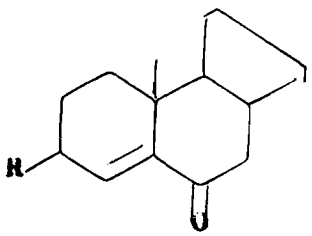
Over the years work has been on in these laboratories concerning the preparation of azasteroids by Schmidt reaction of steroidal ketones and the Beckmann rearrangement of steroidal ketoximes. Previous work was centred on the synthesis of aza-steroids from 3α,5-cyclo-5α-cholestan-6-one (XVII), its 3β-halo-derivatives (XVIII-XX), cholest-4-en-6-one (XXI), its 3β-acetoxy analogue (XXII), cholest-5-en-7-one (XXIII), its 3β-acetoxy analogue (XXIV), cholesta-3,5-dien-7-one (XXV), cholesta-4,6-dien-3-one (XXVI), cholesta-2,4-dien-6-one (XIII), 5α-cholestane-3,6-dione (VI) and cholest-4-ene-3,6-dione (XII).



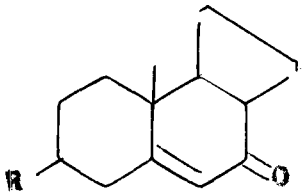
(XVII)



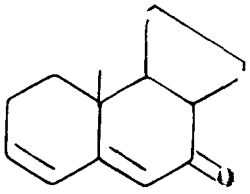
(XVIII) R, Cl
(XIX) R, Br
(XX) R, I



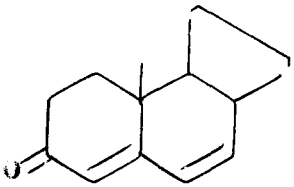
(XXI) R, H
(XXII) R, AcO



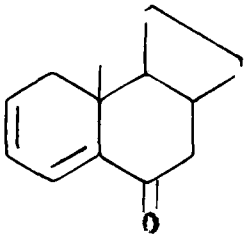
(XXIII) R, H
(XXIV) R, AcO



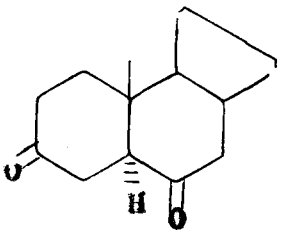
(XXV)



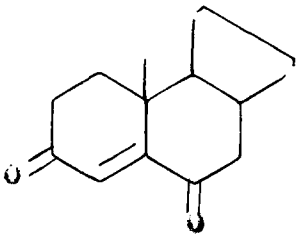
(XXVI)



(XIII)

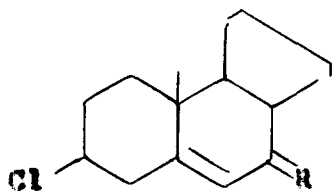


(VI)

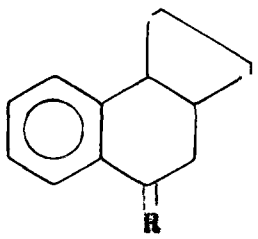


(XII)

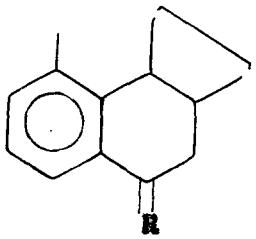
The present work is an extension of the above and employed the hitherto unexplored substrates, 3β-chlorocholest-5-en-7-one (XXVII), its oxime (XXVIII), 19-norcholesta-1,3,5(10)-trien-6-one (XV), its oxime (XXIX), 1-methyl-19-norcholest-1,3,5(10)-trien-6-one (XVI) and its oxime (XXX).



(XXVII) R, O
(XXVIII) R, NOH

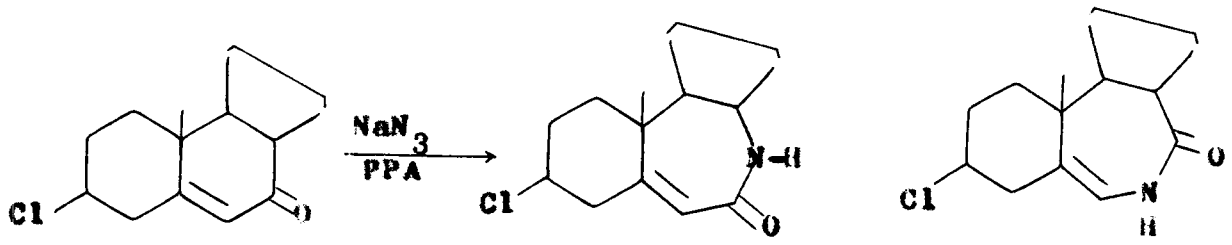


(XV) R, O
(XXIX) R, NOH

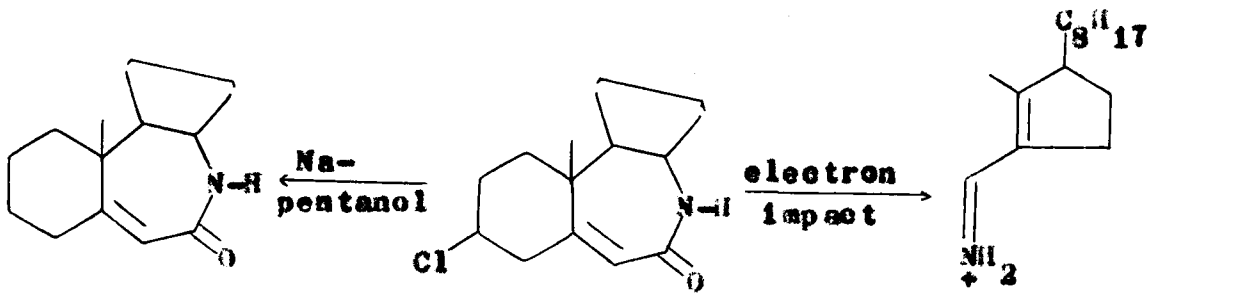


(XVI) R, O
(XXX) R, NOH

The ketone (XXVII) on Schmidt reaction using sodium azide and polyphosphoric acid afforded a single lactam, 3β-chloro-7a-aza-B-homocholest-5-en-7-one (XXXI) distinguishable from its possible isomer (XXXII) on the basis of spectral properties and chemical conversion. In the mass spectrum (XXXI) gave a diagnostic fragment ion peak at m/e 222 ($C_{15}H_{28}N$) as has been observed earlier for 7a-aza lactams in the cholestane series. Chemically the structure was supported by the transformation of (XXXI) into the known lactam 7a-aza-B-homocholest-5-en-7-one (XXXIII) on sodium-pentyl alcohol reduction.

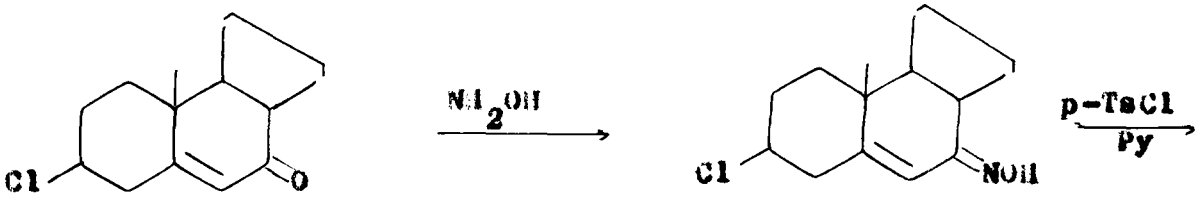


(XXVII) (XXXI) (XXXII)

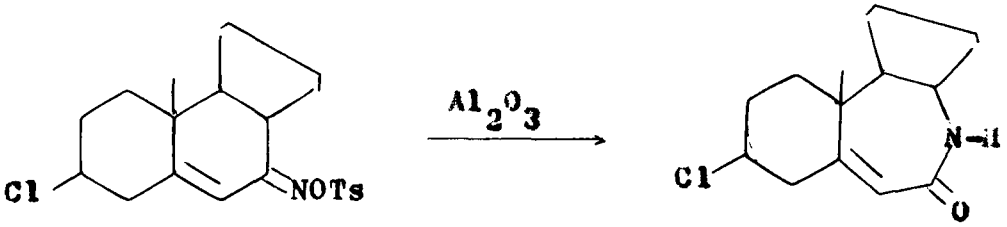


(XXXIII) (XXXI) m/e 222 ($C_{15}H_{28}N$)

The Beckmann rearrangement of the oxime (XXVIII), prepared from the ketone (XXVII) by the usual oximation procedure, using tosylate-alumina procedure also gave the lactam (XXXI) exclusively

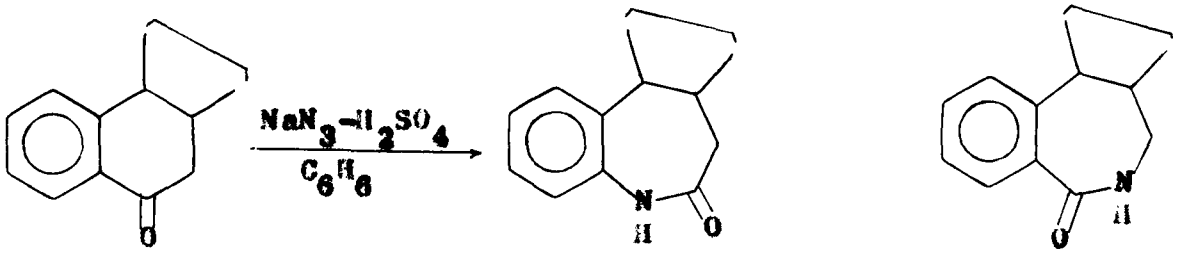


(XXVII) (XXVIII)



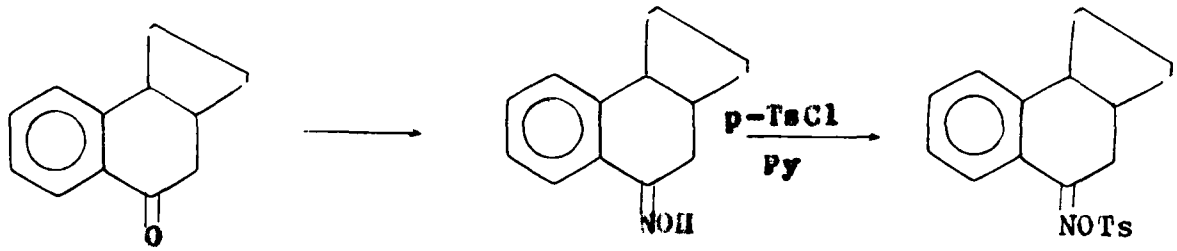
(XXXIV) (XXXI)

The Schmidt reaction of 19-norcholesta-1,3,5(10)-trien-6-one (XV) using sodium azide in benzene and sulphuric acid furnished 19-nor-6-aza-B-homocholesta-1,3,5(10)-trien-7-one (XXXV) and not the isomeric 7-aza-lactam (XXXVI).

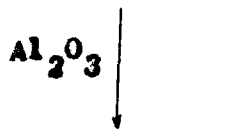


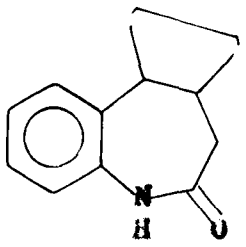
(XV) (XXXV) (XXXVI)

The Beckmann rearrangement of the corresponding oxime (XXIX), first converted into the tosylate (XXXVII) and then rearranged over a column of alumina, provided the same lactam (XXXV).



(XV) (XXIX) (XXXVII)

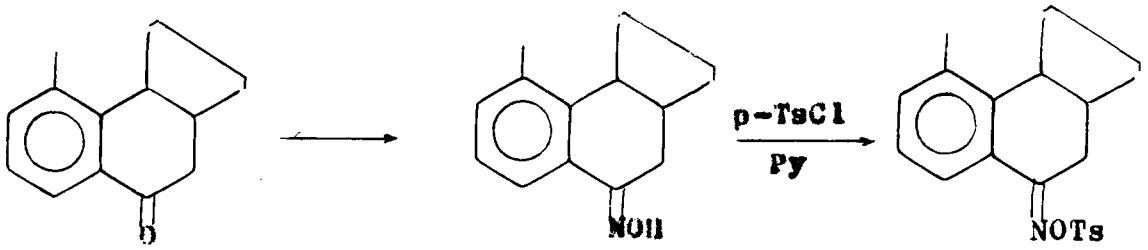




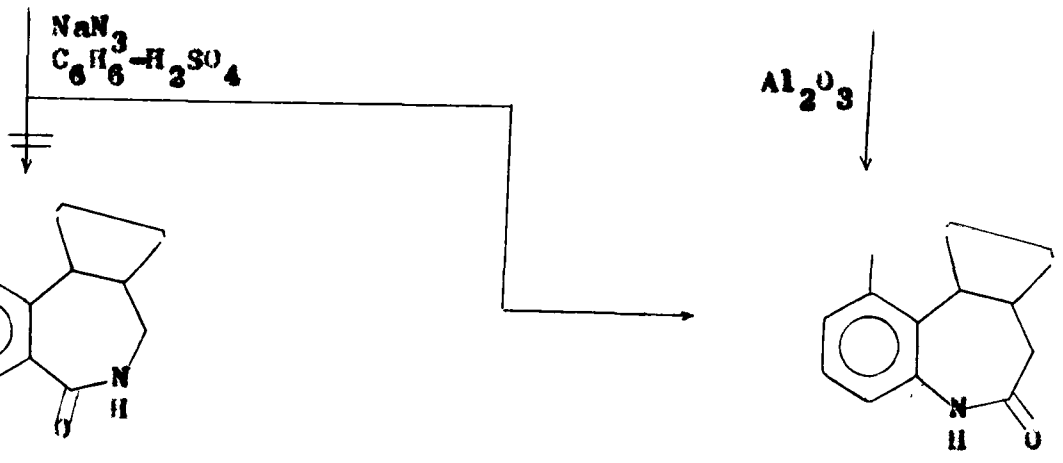
(XXXV)

Similarly, the Schmidt reaction of 1-methyl-19-norcholesta-1,3,5(10)-trien-6-one (XVI) using sodium azide in benzene-sulphuric acid led to entirely the 6-aza lactam, 1-methyl-19-nor-6-aza-B-homocholesta-1,3,5(10)-trien-7-one (XXXVIII) and none of the isomeric 7-aza-lactam (XXXIX).

The Beckmann rearrangement of the oxime (XXX) of the ketone (XVI) by its conversion to the tosylate (XL) and subsequent chromatography over alumina also afforded the lactam (XXXVIII) exclusively.



(XVI) (XXX) (XL)



(XXXIX) (XXXVIII)

The structures have been established on the basis of spectral properties. The study of mass spectral fragmentation of (XV), (XVI), (XXVII-XXXI), (XXXV) and (XXXVIII) have been made with a view to arrive at useful spectra-structure correlationships.

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1977

Department of Chemistry
Aligarh Muslim University
Aligarh

This is to certify that the work described in this thesis is the original work of the candidate done under my supervision. The thesis is suitable for submission for the award of the degree of Doctor of Philosophy in Chemistry.

Sullah

(Shafiullah)
Ph.D.
Lecturer in Chemistry

ACKNOWLEDGEMENTS

I am extremely grateful to Prof. M.S. Ahmad but for whose generous help right from the beginning this work could not have seen an end. His contribution is enormous and invaluable. I am also indebted to Dr. Shafiullah for his guidance. My thanks are also due to Prof. W. Rahman, Head, Department of Chemistry, for providing necessary facilities and for occasional encouragement. Financial assistance from U.G.C. (Local) is gratefully acknowledged.

In the end I would like to show my appreciation of the help that I received from my research colleagues, and Mr. I.A. Jilani's patience while doing the exhaustive work of typing the thesis.

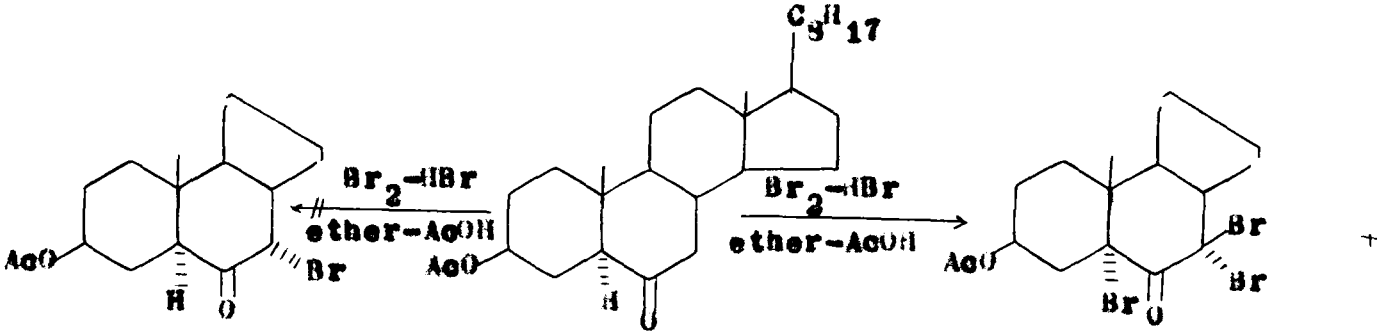
ISLAMUDDIN

C O N T E N T S

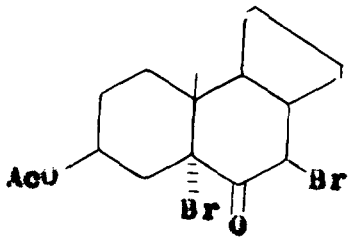
SUMMARY

PART - I (α-Bromination)

Previous work in these laboratories on α-bromination was concerned with an attempted preparation of 3β-acetoxy-7α-bromo-5α-cholestan-6-one (II) from 3β-acetoxy-5α-cholestan-6-one (I) which on treatment with Br_2-HBr in ether-acetic acid invariably afforded 3β-acetoxy-5,7,7-tribromo-5α-cholestan-6-one (III) and, in one or two experiment under similar conditions, 3β-acetoxy-5,7β-dibromo-5α-cholestan-6-one (IV). None of the products was found to be the desired 7α-bromoketone (II).

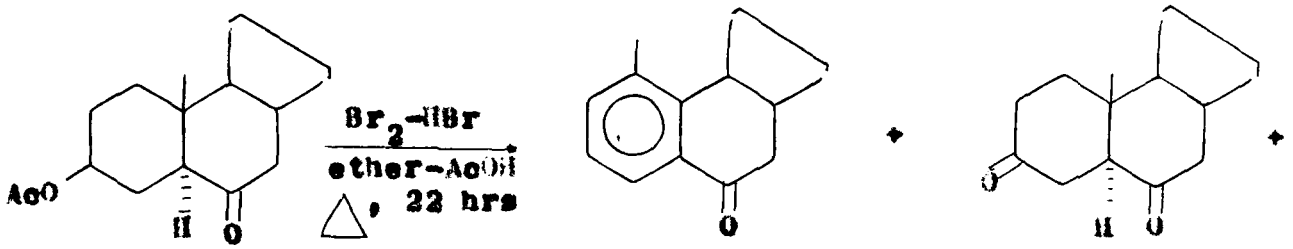


(II) (I) (III)

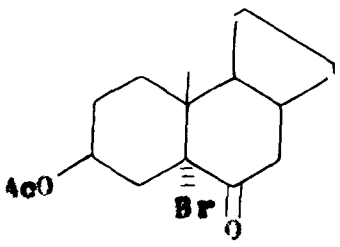


(IV)

In a continued effort to obtain (II), the ketone (I) was heated under reflux with Br_2 and HBr in ether-acetic acid which also failed to provide (II) but interestingly gave 1-methyl-19-norcholesta-1,3,5(10)-trien-6-one (V), a product of A-ring aromatisation alongwith 5α-cholestane-3,6-dione (VI) and 3β-acetoxy-5-bromo-5α-cholestan-6-one (VII), which was shown to be an intermediate in the conversion of (I) into (V).

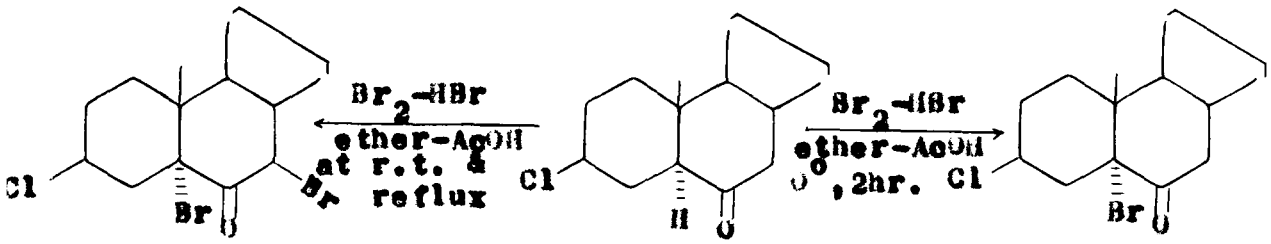


(I) (V) (VI)



(VII)

In continuation of the above work and in anticipation of obtaining some interesting results, 3β-chloro-5α-cholestan-6-one (VIII) was subjected to α-bromination under varying conditions. Reaction of (I) with bromine and HBr in ether-acetic acid in cold repeatedly gave 3β-chloro-5-bromo-3α-cholestan-6-one (IX). Bromination of the ketone (VIII) under essentially the same conditions of solvents and reagents but at room temperature and reflux temperature gave a different product of bromination, 3β-chloro-5,7β-dibromo-5α-cholestan-6-one (X). In no case we could obtain the product of ring A-aromatization of which we were desirous.

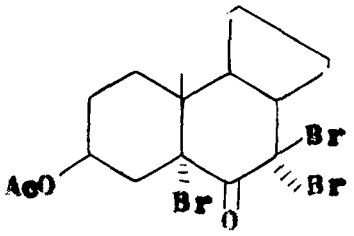


(X) (VIII) (IX)

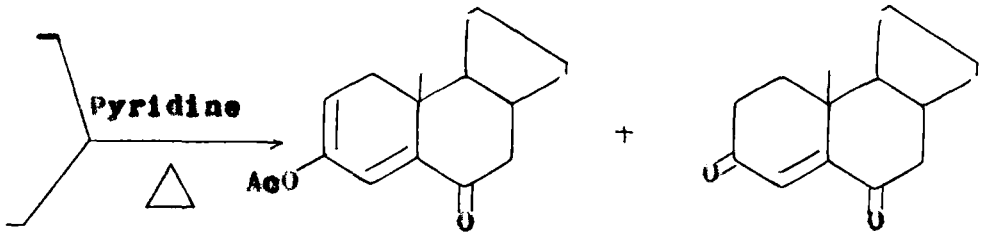
PART - II (Aromatization via Dehydrohalogenation)

Concerning this subject it was previously noted that (III) and (IV) under reflux with pyridine provided 3-acetoxy-cholesta-2,4-dien-6-one (XI) and cholest-4-ene-3,6-dione (XII)

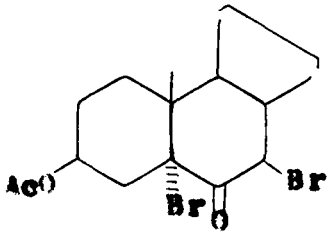
but none of the aromatized products which quite often result from pyridine-induced dehydrohalogenation of haloketosteroids.



(III)



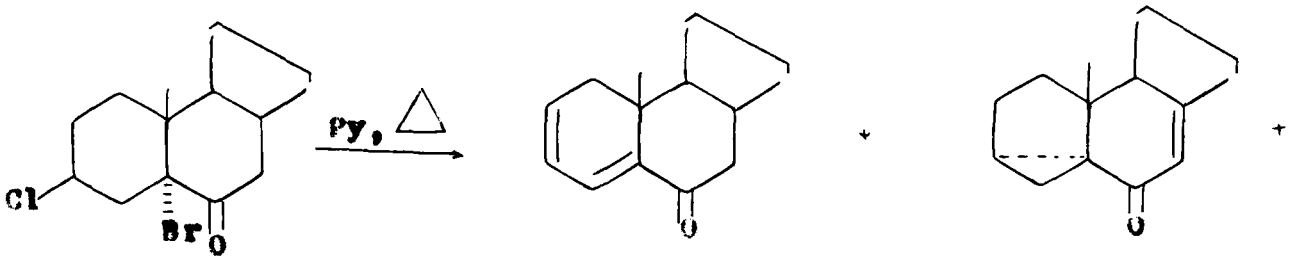
(XI) (XII)



(IV)

Following these lines we also subjected 3β-chloro-5-bromo-5α-cholestan-6-one (IX) to dehydrohalogenation with pyridine under reflux. The aim of obtaining product of ring-A aromatization was successfully achieved in this reaction which provided cholesta-2,4-dien-6-one (XIII), 5α-cholestane-3,6-dione (VI),

3α,5-cyclo-5α-cholest-7-en-6-one (XIV) and the aromatized product, 19-norcholesta-1,3,5(10)-trien-6-one (XV). Structures have been established making use of their spectral properties, especially characteristic mass spectral fragmentation of each compound.

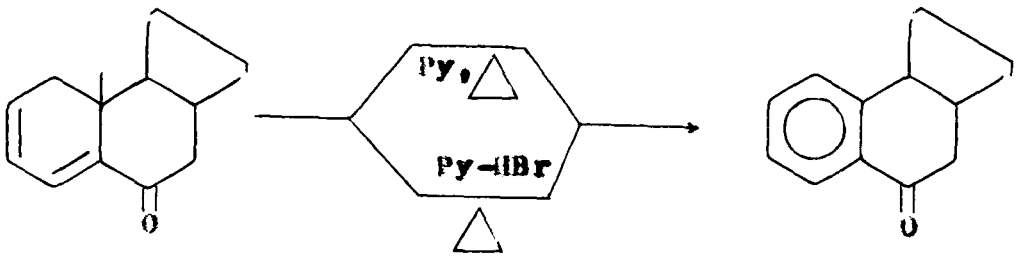


(IX) (XIII) (XIV)

(VI) (XV)

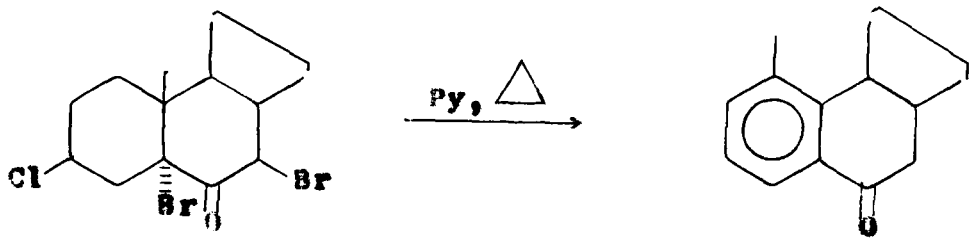
Mechanistic pathways have been suggested for the formation of the products (XIII), (VI), (XIV) and (XV) from (IX). The formation of the dienone (XIII) is a case of straightforward dehydrohalogenation of (IX). It has been suggested that traces

of water present in pyridine play a subtle role in the production of the dione (VI). The conversion of (IX) into (XIV) requires initial isomerisation of bromine from C5(α) to C7(α or β) and then dehydrohalogenation occurs during the course of the reaction. Regarding the aromatisation it has been shown by experiment that the dienone (XIII) is the immediate precursor of the aromatised product (XV) since (XIII) under reflux with pyridine alone failed to give (XV) but in the additional presence of catalytic amounts of HBr (XIII) smoothly provided (XV), thereby supporting the proposed mechanism involving loss of C10-methyl group as methane.



(XIII) (XV)

When 3β-chloro-5,7β-dibromo-5α-cholestan-6-one (X) was refluxed with pyridine it furnished a product of ring A aromatization attended by methyl migration from C10 to C1, 1-methyl-19-norcholesta-1,3,5(10)-trien-6-one (XVI).

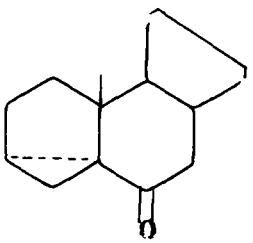


(X) (XVI)

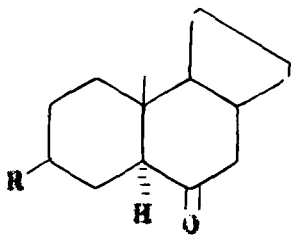
The mechanism proposed for this transformation finds analogy with those which have been established as a result of previous such studies.

PART - III (Azasteroids)

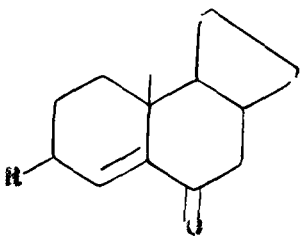
Over the years work has been on in these laboratories concerning the preparation of azasteroids by Schmidt reaction of steroidal ketones and the Beckmann rearrangement of steroidal ketoximes. Previous work was centred on the synthesis of azasteroids from 3α,5-cyclo-5α-cholestan-6-one (XVII), its 3β-halo-derivatives (XVIII-XX), cholest-4-en-6-one (XXI), its 3β-acetoxy analogue (XXII), cholest-5-en-7-one (XXIII), its 3β-acetoxy analogue (XXIV), cholesta-3,5-dien-7-one (XXV), cholesta-4,6-dien-3-one (XXVI), cholesta-2,4-dien-6-one (XIII), 5α-cholestane-3,6-dione (VI) and cholest-4-ene-3,6-dione (XII).



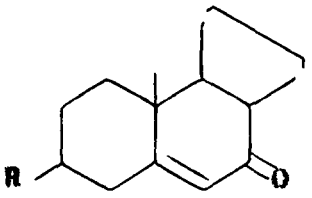
(XVII)



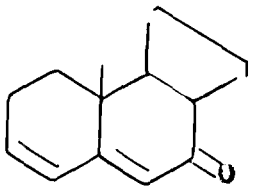
(XVIII) R, Cl
(XIX) R, Br
(XX) R, I



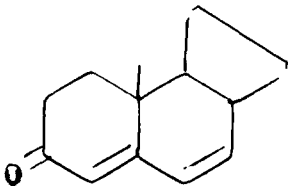
(XXI) R, H
(XXII) R, AcO



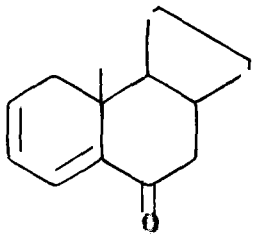
(XXIII) R, H
(XXIV) R, AcO



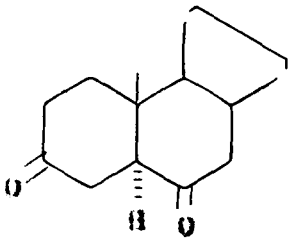
(XXV)



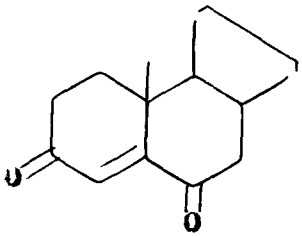
(XXVI)



(XIII)

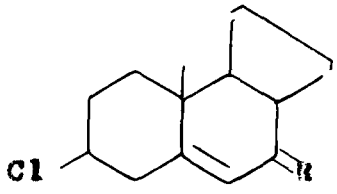


(VI)

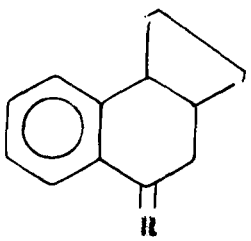


(XII)

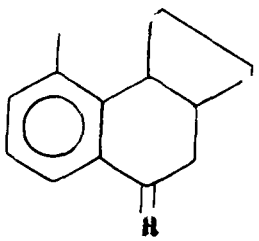
The present work is an extension of the above and employed the hitherto unexplored substrates, 3β-chlorocholest-5-en-7-one (XXVII), its oxime (XXVIII), 19-norcholesta-1,3,5(10)-trien-6-one (XV), its oxime (XXIX), 1-methyl-19-norcholest-1,3,5(10)-trien-6-one (XVI) and its oxime (XXX).



(XXVII) R, O
(XXVIII) R, NOH

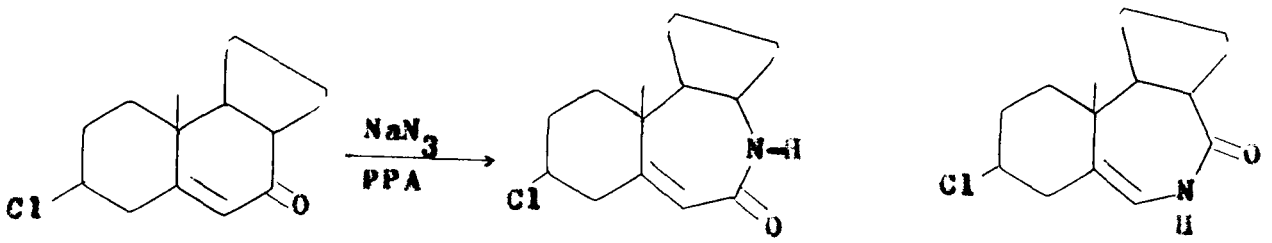


(XV) R, O
(XXIX) R, NOH

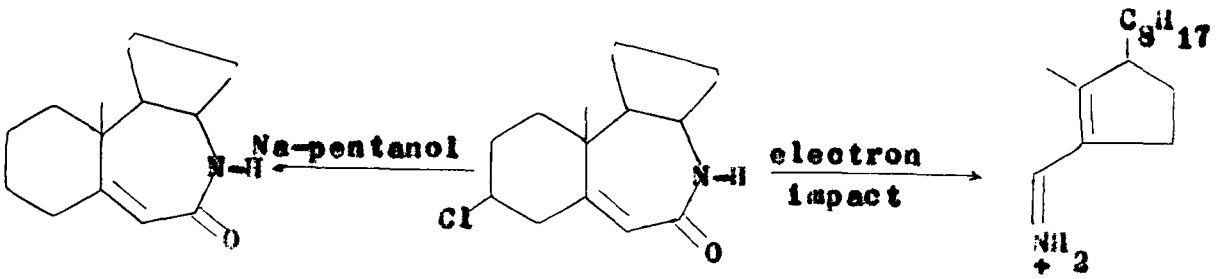


(XVI) R, O
(XXX) R, NOH

The ketone (XXVII) on Schmidt reaction using sodium azide and polyphosphoric acid afforded a single lactam, 3β-chloro-7a-aza-B-homocholest-5-en-7-one (XXXI) distinguishable from its possible isomer (XXXII) on the basis of spectral properties and chemical conversion. In the mass spectrum (XXXI) gave a diagnostic fragment ion peak at m/e 222 ($C_{15}H_{28}N$) as has been observed earlier for 7a-aza lactams in the cholestane series. Chemically the structure was supported by the transformation of (XXXI) into the known lactam 7a-aza-B-homocholest-5-en-7-one (XXXIII) on sodium-pentyl alcohol reduction.

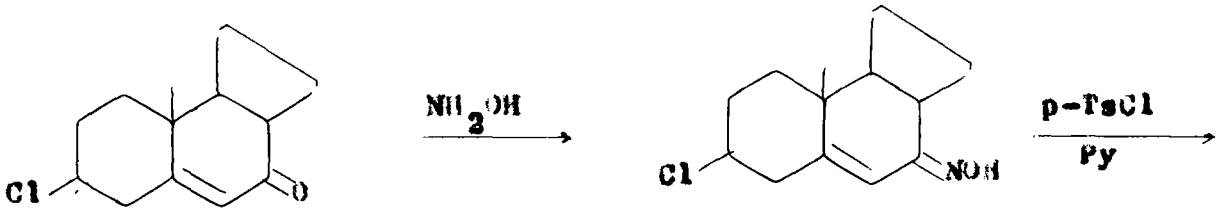


(XXVII) (XXXI) (XXXII)

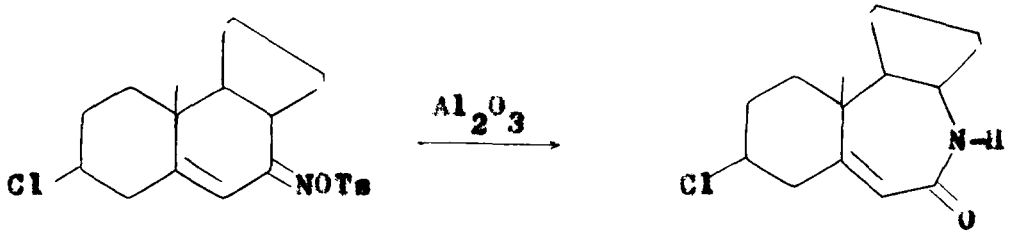


(XXXIII) (XXXI) m/e 222 ($C_{15}H_{28}N$)

The Beckmann rearrangement of the oxime (XXVIII), prepared from the ketone (XXVII) by the usual oximation procedure, using tosylate-alumina procedure also gave the lactam (XXXI) exclusively.

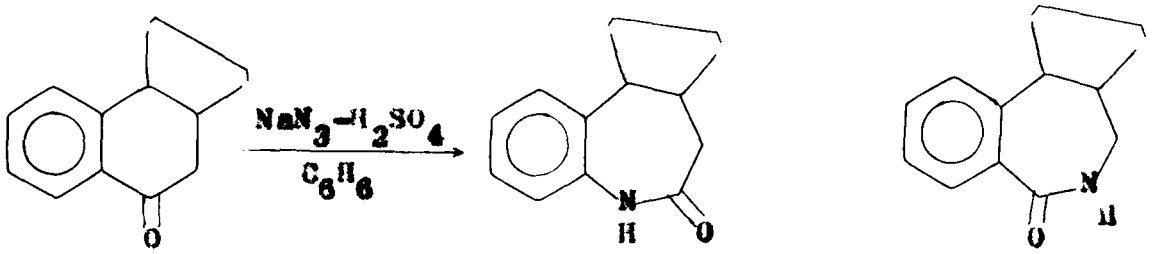


(XXVII) (XXVIII)



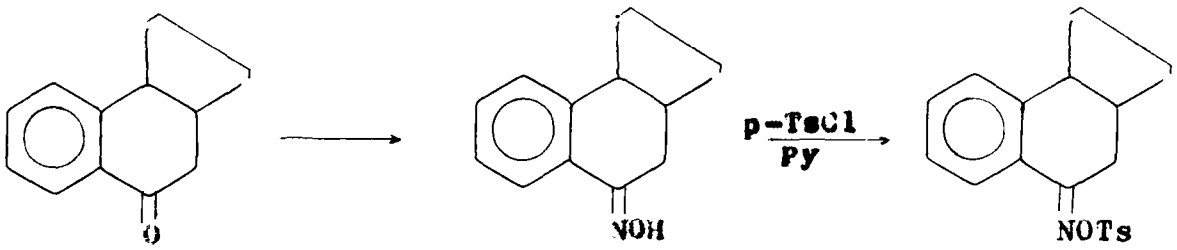
(XXXIV) (XXXI)

The Schmidt reaction of 19-norcholesta-1,3,5(10)-trien-6-one (XV) using sodium azide in benzene and sulphuric acid furnished 19-nor-6-aza-8-homocholesta-1,3,5(10)-trien-7-one (XXXV) and not the isomeric 7-aza-lactam (XXXVI).

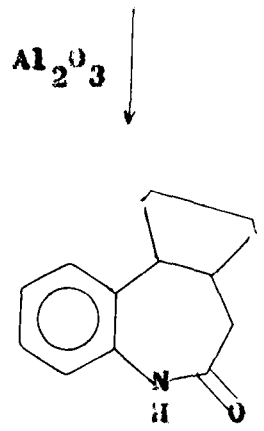


(XV) (XXXV) (XXXVI)

The Beckmann rearrangement of the corresponding oxime (XXIX), first converted into the tosylate (XXXVII) and then rearranged over a column of alumina, provided the same lactam (XXXV).



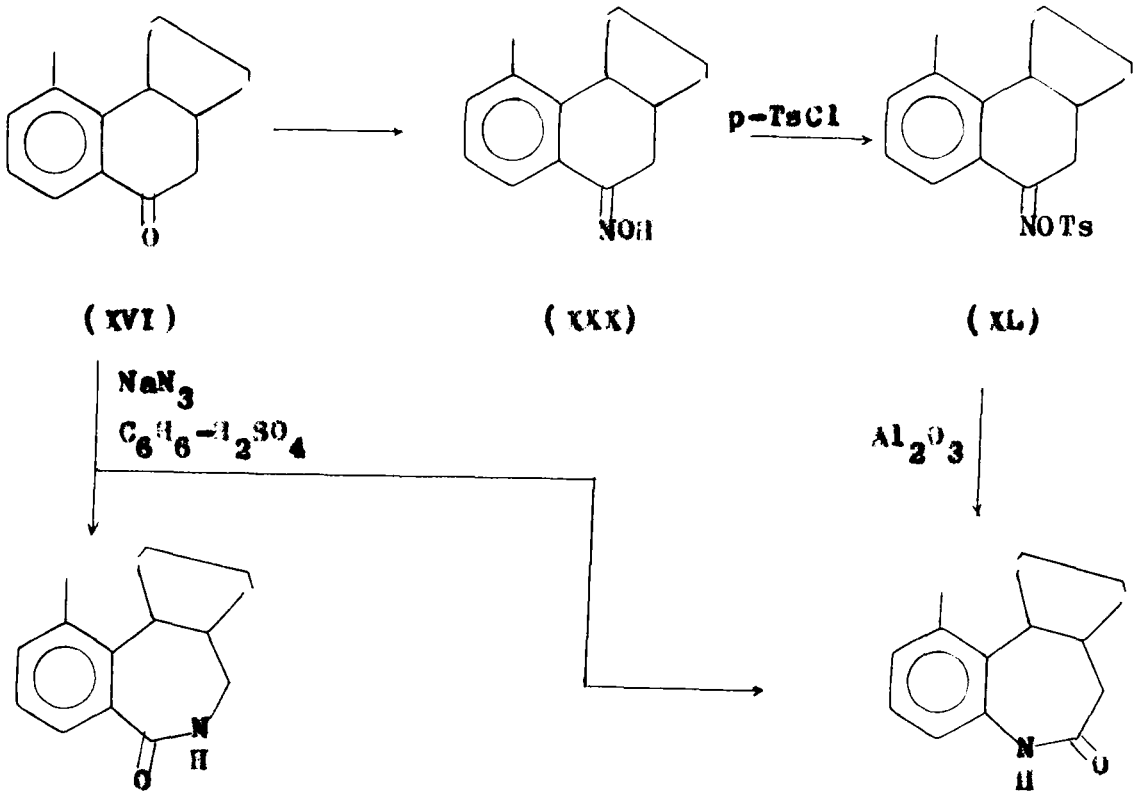
(XV) (XXIX) (XXXVII)



(XXXV)

Similarly, the Schmidt reaction of 1-methyl-19-norcholesta-1,3,5(10)-trien-6-one (XVI) using sodium azide in benzene-sulphuric acid led to entirely the 6-aza lactam, 1-methyl-19-nor-6-aza-B-homocholesta-1,3,5(10)-trien-7-one (XXXVIII) and none of the isomeric 7-aza-lactam (XXXIX).

The Beckmann rearrangement of the oxime (XXX) of the ketone (XVI) by its conversion to the tosylate (XL) and subsequent chromatography over alumina also afforded the lactam (XXXVIII) exclusively.



(XVI) (XXX) (XL)

(XXXIX) (XXXVIII)

The structures have been established on the basis of spectral properties. The study of mass spectral fragmentation of (XV), (XVI), (XXVII-XXXI), (XXXV) and (XXXVIII) have been made with a view to arrive at useful spectra-structure correlationships.

THEORETICAL

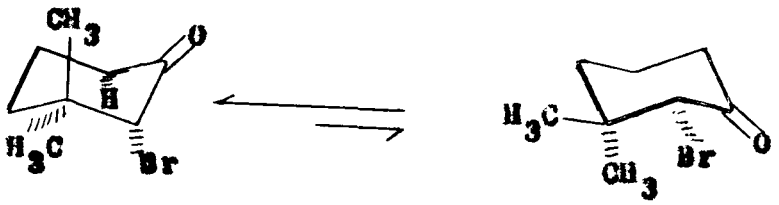
α-Bromination of Ketones

The bromination of ketones as it is ordinarily conducted, namely, in the presence of added or generated hydrogen bromide, results in the thermodynamically more stable product. Kinetically controlled bromination may be effected by carrying out the reaction in the presence of an agent capable of removing hydrogen bromide as it is formed, e.g. sodium acetate, or by brominating the corresponding enol acetate in the presence of pyridine, sodium acetate or epichlorohydrin. The kinetic product may be the same[1] as the thermodynamic one or different[2,3] from it depending on steric factors.

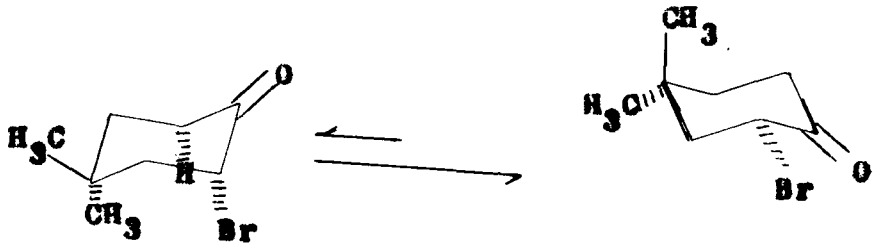
α-Bromination of methylene and methyl ketones in the presence of base cannot be stopped at the monobromoketone stage. The polybromoketones thus formed are cleaved under the basic conditions to form haloform and carboxylic acid.

Since the isolated cyclohexane ring is non-rigid and can flip from one chair form to another more stable chair conformation, a 2-bromocyclohexanone is free to assume whichever chair conformation affords maximum stability to the molecule. Corey[5,6], using infrared spectroscopy, deduced the stable orientation of a series of methylated 2-bromocyclohexanones and observed that orientation of bromine in stable conformation is sometimes axial and sometimes

equatorial. Thus in the case of 2-bromo-3,3-dimethylcyclohexanone, the stable conformation is with bromine as axial (a-I) and in the 4,4-dimethylisomer the bromine is equatorially oriented (e-II). The thermodynamically controlled α-bromocyclohexanone involves electrical repulsion between carbon-oxygen and carbon-bromine dipoles and destabilises the bromine in equatorial position from the isomer with bromine in axial position. On the other hand, steric effect (1:3 H:Br interaction) which is at the maximum when bromine is axial, destabilises the bromine in axial form.



(a-I) (e-I)

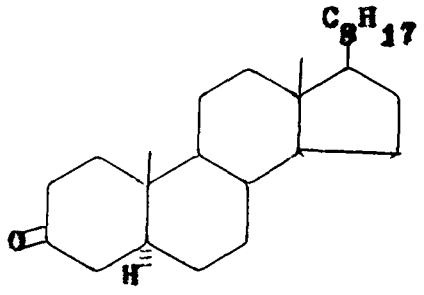


(a-II) (e-II)

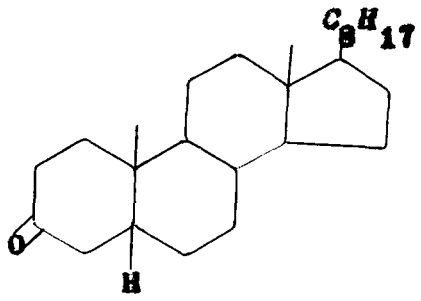
Electrical repulsion is estimated to destabilise (e-I) to the extent of some 2.7 Kcal/mol, while steric interaction destabilises (a-I) by only about 0.4 Kcal/mol. Since the

electrical repulsions are relatively constant, the magnitude of the steric effect involving axial bromine will determine the orientation of bromine in the stable form. Thus in 2-bromo-4,4-dimethylcyclohexanone, the steric repulsion between axial bromine and axial methyl in (a-II) dominates over electrical effect in (e-II) and the bromine in equatorial position is the more stable one.

A steroid bromoketone is rigid in the sense that ring flip is not possible, and the conformation of maximum stability is not attained automatically. Indeed, a few of the bromoketosteroids in both labile and stable forms, usually recognisable from observation that under catalysis by hydrogen bromide the former can be isomerised to the latter; these compounds are all of the type-CHBrCO-, and equilibration is achieved through the enol form. From the relative importance of electrical and steric repulsions based on stability relationship in the cyclohexane series, Corey[5] deduced the relative stabilities of the epimeric bromo derivatives of 5α-cholestan-3-one (III) and 5β-cholestan-3-one(IV).

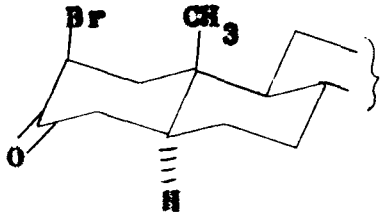


(III)

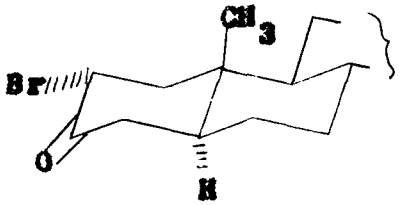


(IV)

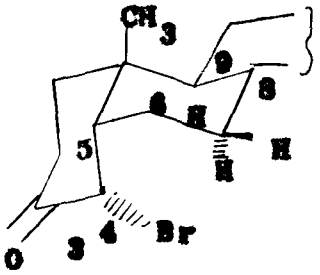
Thus 2β-bromocholestan-3-one (a-V) is destabilised by a Br:CH_3 interaction, and 4 -bromo-5 -cholestan-3-one (a-VI) is subject to interaction of bromine with carbon atom (C-7 and C-9), and the product of expected greater stability, 2∝-bromo-5∝-cholestan-3-one (e-V) and 4β-bromo-5β-cholestan-3-one (e-VI) are indeed stable epimers that have been isolated as bromination products.



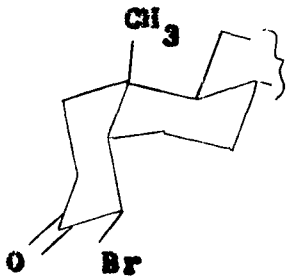
(a-V)



(e-V)



(a-VI)



(e-VI)

Corey[7,8] noticed that in those instances where both labile and stable epimers have been isolated, the initially formed labile compound is with bromine in axial position, an indication that the axial epimer is formed faster than the equatorial one. Thus it is assumed that in the bromination of 5∝-cholestan-3-one (III)

and 5β-cholestan-3-one (IV) the axial epimers are the initial products but are so labile that they have escaped isolation.

Two interpretation that have been advanced for preferential axial bromination are formulated for the case of cyclohexanone, where reacting species is the enol of half chair conformation (IX). Corey[7,8] noted that in the formation of axial product (VIII), but not of the equatorial isomer, the π-orbitals of the enol are arranged favourably for efficient overlap in the transition state with an orbital left vacant by the leaving α-hydrogen atom. An alternative explanation[9] is that the reaction involves a cyclic bromonium ion (α or β), which by diaxial opening (X) and elimination affords the axial α-bromoketone and is shown in Fig. 1.

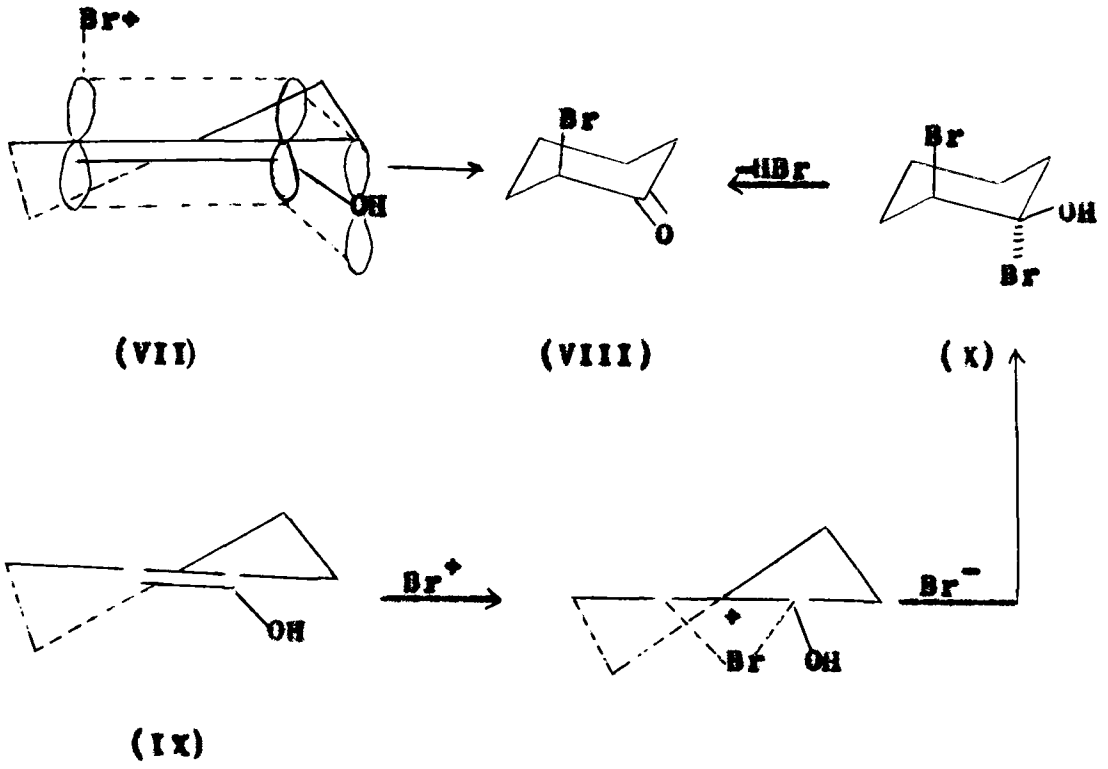
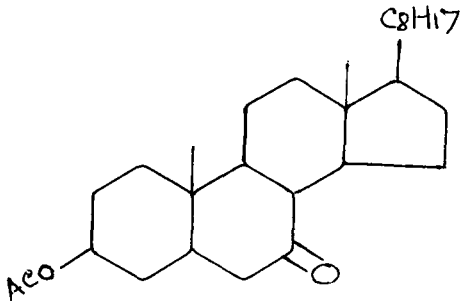


Fig. 1

The stereochemistry of the enolization of 3β-acetoxycholestan-7-one (XI) to the Δ^6-en-7-ol and of the ketonization of this enol have been studied using deuterium tracer with hydrogen bromide as catalyst in chloroform solution. The axial hydrogen at C-6 is lost in enolization 1-2 times as rapidly as the equatorial hydrogen. For the reverse reaction, ketonization, an axial hydrogen is gained about 1.5 times as rapidly as an equatorial hydrogen. The values indicate that despite strong steric repulsion of the gain and loss of axial hydrogen, axial attack is still favourable over equatorial attack. Correction for this steric effect gives the result that 'stereoelectronic factors' favour axial attack over equatorial attack by a factor of at least 12. The acetic acid catalysed enolization-ketonization[10-13] reaction is even more specific and axial attack is favoured over equatorial attack by a total factor of at least 9 with a stereoelectronic component of at least 50.

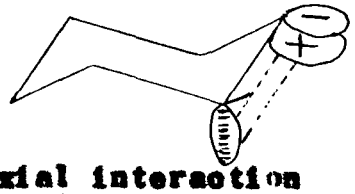


(XI)

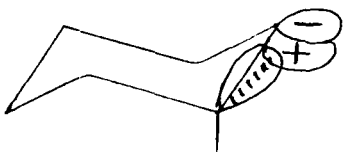
α-Bromination of steroid ketones via the corresponding enols is characterized in several cases, and perhaps generally, by an effect which directs the incoming bromine substituent to

the axial rather than the equatorial position. Opposing this effect is classical steric effect which directs a large substituent such as bromine to the less crowded equatorial orientation. The net result of these two effects which influence the relative rates of formation of the epimers with axial and equatorial bromine is clear on those cases where the bromoketone which is isolated as the unstable epimer, formed for kinetic rather than for steady-state reasons. In such instances the importance of the non steric effect is apparent since the major product has invariably been found to be the epimer with axial bromine.

Orienting influence which is responsible for this stereochemical preference is stereochemical-electronic in nature and depends on the difference in degree of delocalization of electrons in perturbed axial and equatorial bonds which are α- to an exocyclic π -orbital. The following figure indicates the relationship between stereochemical orientation and the extent of delocalization of exocyclic σ -electrons to an adjacent exocyclic π -orbital. Since the transition state for enolization-ketonization type processes is stabilised by bonding between the α- carbon and carbonyl carbon atom involving σ-π delocalization as shown in Fig. II. There should be a preference for loss or gain of an axial



axial interaction
(bonding)



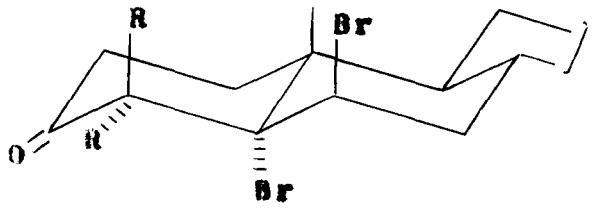
equatorial interaction
(non-bonding)

Fig. II

α-substituent over an equatorial α-substituent, or in slightly different terms, there is a better bonding in the transition state for enolization-ketonization when the entering or leaving α-substituent possess the axial orientation rather than the alternative equatorial orientation. Because the structure of the transition state for such processes is intermediate between the structures of the enol and ketone or ketone conjugate acid, the bond being formed to or broken from α-carbon will not possess pure axial or equatorial character and the considerations expressed in Fig. II are extreme. However, as the transition state structure approaches that of the ketone, the magnitude of the stereoelectronic discrimination[14,16] should increase in favour of axial attack.

Corey[7,8] has reported the methods for predicting the orientation of bromine in all α-bromoketosteroids with ketone function in ring A, B or C and A/B ring junction trans or cis. One method applies to α-bromoketosteroids whose stereochemistry is thermodynamically controlled and the other method applies to α-bromoketosteroids whose stereochemistry is kinetically controlled. In every case there is an agreement between predicted and determined configuration at (CBr). Thus Butenandt and coworkers[17,18] reported that the bromination of 3α,6β-dibromocholestan-3-one (XII) in acetic acid produces 4β-epimer(XIII), while Inhoffen[19,20] reported that the bromination of the same ketone (XII) in ether-acetic acid produces a 4α-epimer (XIV). Corey[7,8] has been able to obtain 4α-epimer (XIV) in good yield by isomerization of the 4β-

epimer (XIII) with ethereal hydrogen chloride and suggested that former is the stable epimer and the product of thermodynamic control, while the latter is the unstable epimer and the product of kinetic control.



(XII) R=R'=H
(XIII) R=Br; R'=H
(XIV) R'=Br; R=H

The Kinetically controlled Bromination Products

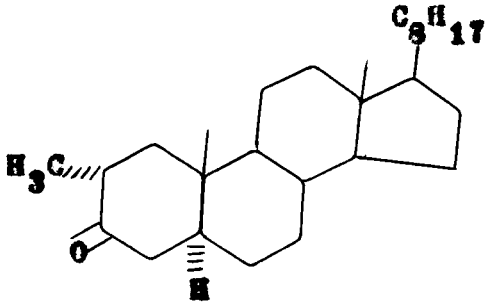
Corey[7,8] has developed a rule for predicting the stereochemistry of the kinetically controlled bromination products of ketosteroids. According to rule: the epimer which is formed faster in the bromination of ketosteroid is that in which bromine is axial.

A better understanding of the rule may be had by considering the theoretical basis upon which it was derived. Ketonization of an enol and reverse reaction, enolization of a ketone, proceed through the same transition state and hence the same geometrical requirements for minimizing the energy of the transition state hold for both reactions. The energy of the transition state for enolization will be at minimum when there is maximum opportunity

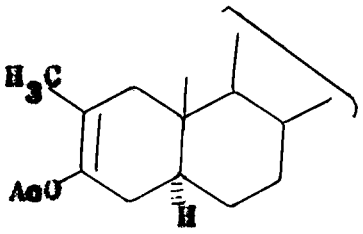
for bond formation between the $Sp^3 \rightarrow p$ orbital made available by the leaving hydrogen and the p-orbital of the carbonyl carbon.

In the case of cyclohexanone this implies that in enolisation, an axial α-hydrogen is lost in preference to an equatorial α-hydrogen. Furthermore, it follows that in the ketonisation of an enolised cyclohexanone (e.g. bromination or protonation) the incoming substituent should adopt preferentially the axial orientation.

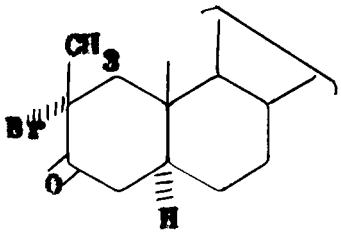
Kinetically controlled bromination[21] in the presence of pyridine of the enol acetate (XVI) of 2α-methyl-5α-cholestan-3-one (XV)[22,23] yields 2α-bromo-2β-methyl-5α-cholestan-3-one (XVII) in which ring A exists in the boat conformation (XXI)[24-26]. The hydrogen bromide promoted equilibration of (XVII) which led to the thermodynamically more stable 2β-bromo-2α-methyl-5α-cholestan-3-one (XVIII) accompanied by the rearrangement product 2α-methyl-4α-bromocholestan-3-one (XIX). Thus it was concluded in the light of Corey's generalisation[5-8,27] that kinetically controlled bromination product is (XVII) with A ring in the boat form (XXI), while the thermodynamically preferred one is the (XVIII) with unchanged chair conformation in ring A (XXII). It is interesting to note that the boat form (XXI) is energetically preferred over its chair form (XX). The energy differences involved must be of a fairly small order of magnitude and the chief role is clearly played by the angular methyl group, since the situation is completely altered upon its removal.



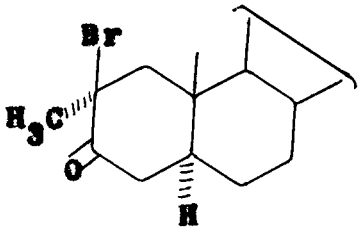
(XV)



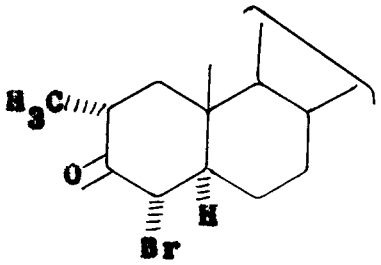
(XVI)



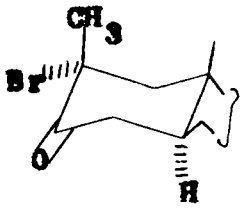
(XVII)



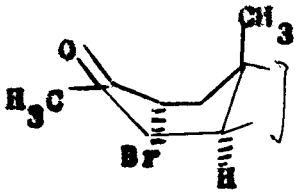
(XVIII)



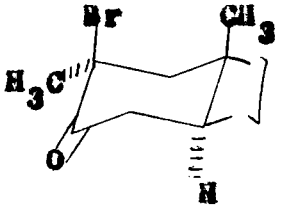
(XIX)



(XX)



(XXI)



(XXII)

The bromoketone (XVII) in the boat form (XXI) under conditions of kinetic control possess axial bromine. It would be consistent with the view[5-8] that kinetic control always involves axial attack or due to equatorial attack of bromine in an intermediate of chair-like conformation. In either event rearward approach of bromine is required rather the implied topside entry which leads to the incorrect structure (XVIII). The other alternative[25] suggests the formation of equatorial 2∝-bromoketone (XVII with a chair form (XX) of ring A and that undergoes conformational "flip" to the boat form (XXI) in order to minimize the unfavourable steric and electrostatic factors in (XX).

Spectral approach to ∝-brominated ketosteroids

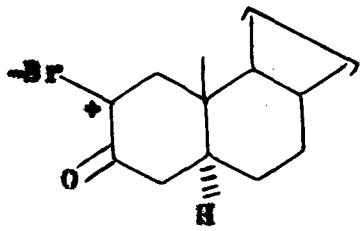
I.R. Spectroscopy

The frequency[9] and intensity of the carbonyl stretching bands in ketosteroids[28-33] are influenced by bromination at an adjacent methylene group, and the effect of such ∝-bromination depends on the stereochemical aspects of the carbon-bromine bond. The introduction of a single bromine atom increases the frequency of carbonyl maximum by 13-19 cm^{-1} and depresses the integrated absorption intensity by about 25%. The introduction of second bromine atom at the same ∝-carbon atom to form a dibromide produces little further change in the carbonyl frequency, but if a second bromine atom is introduced on the ∝′-methylene group,

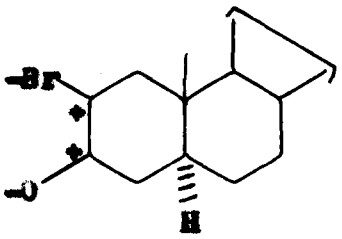
to yield 2,4-dibromoketone, an additional increase of about 20 cm^{-1} occurs in the carbonyl frequency and the intensity is further depressed. A positive frequency shift is observed also in 6-bromo-7-ketone and is shown in Table I. There are three factors which might be expected to influence the vibrational frequency of the carbonyl band when a bromine atom is substituted at the α-carbon atom; (i) a mass effect, (ii) an electromeric effect transmitted from the C-Br bond through the C-C bond to the C=O bond and (iii) coulombic field effect produced by the C-Br dipole on the C=O bond.

It seems highly unlikely that an increase in the carbonyl frequency could be explained by a mass effect when a light hydrogen atom is replaced by a heavy bromine atom. No definite conclusions can be reached about this without carrying out a normal coordinate analysis of the vibrations, but it is also discounted by the fact that an α-iodine substituent produces a smaller frequency displacement than an α-bromine substituent. If the A ring of the steroid nucleus is regarded as cyclohexanone ring in the conventional "Chair" conformation the carbonyl group at position 3 lies approximately in the plane of the ring, and two C-H bonds at positions 2 are arranged so that while one lies approximately in the plane of the ring (equatorial bond) the other is perpendicular to this plane (the axial bond)[39]. A similar disposition exists at carbon atom 4. If a bromine atom is introduced at position 2 in the equatorial position, the C-Br bond and C=O bonds will be

approximately coplanar and the polarity of the C-Br bond suppressing the contribution of structure (XXIIIb) to the resonance. This would raise the frequency of the carbonyl vibration. If, on the other hand, the bromine atom is substituted at axial position, the C-Br and C=O dipoles lie approximately perpendicular to one



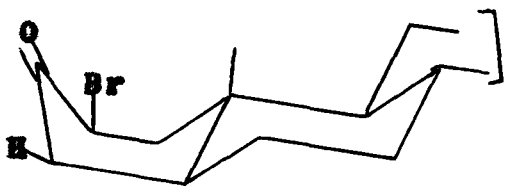
(XXIIIa)



(XXIIIb)

another and the field effect and accompanying change of vibration frequency would be expected to be small.

If, in the 2- and 4-bromo-3-ketones, A ring adopts a boat form, the carbonyl group can be inclined steeply to the main plane of the ring, and the sharp distinction between the effects of axial and equatorial C-Br bond on the C=O bond polarisation may no longer be observed.



(XXIV)

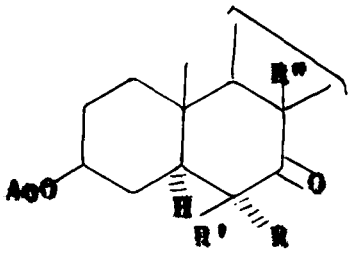
Table - I

Carbonyl band positions and steric configurations for α-brominated ketosteroids

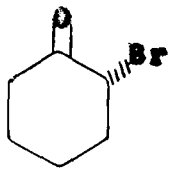
Compounds	Carbonyl position cm^{-1}	Band intensity	Frequency shift on bromination.	Conformation of C-Br bond	Configuration of C-Br bond	Ref.
5 -Cholestan-3-one	1715	2.62	-	-	-	9
2-Bromocholestan-3-one	1733	1.99	15	e	α	9
2,2-Dibromocholestan-3-one	1735	1.83	17	e,a	α,β	9
2,4-Dibromocholestan-3-one	1756	1.23	38	e,e	α,α	9,34-35
Coprostan-3-one	1716	-	-	-	-	9
4-Bromocoprostan-3-one	1733	1.87	17	e	β	9
2,4-Dibromocoprostan-3-one	1756	-	40	e,e	$\beta\beta$	9,36-37
3β-Acetoxy-5--cholestan-6-one	1718	-	4	-	-	7
3β-Acetoxy-5 -bromocholestan-6-one	1711	-	4	a	α	7
3β-Acetoxy-7 -bromo-5 -cholestan-6-one	1713	-	2	a	α	7
3β-Acetoxy-5 ,7 -dibromocholestan-6-one	1708	-	-3	a,a	α,α	7
3β-Acetoxy-5 ,7 -dibromocholestan-6-one	1727	-	16	a,e	α,β	7

U.V. Spectroscopy

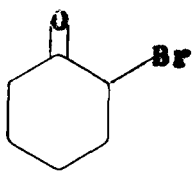
The configuration of the C-Br bond appears also to influence the position and intensity of the U.V. absorption band of the carbonyl chromophores. In 1938, Heilbron and coworkers[39] reported that the introduction of an equatorial bromine atom in 6α-bromo-isomer (XXV), produces a hypsochromic shift of about 30 nm. On the other hand, introduction of an axially oriented bromine as in 6β-bromoisomer (XXVI) is characterized by a bathochromic shift of about 25 nm. Axial substitution on the other side of the carbonyl group as in 8β-isomer (XXVII) results in precisely the same type of the bathochromic shift as recorded for the axial 6β-isomer (XXVI). Cookson[40] has reported a bathochromic shift of about 28 nm in ultraviolet absorption maxima of an axial α-bromocyclohexanone (XXVIII) while a slight hypsochromic change (3 nm) is noted with the corresponding equatorial isomer (XXIX)[41].



(XXV) R=Br; R'=R''=H
(XXVI) R=R''=H; R'=Br
(XXVII) R=R'=H; R''=Br



(XXVIII)



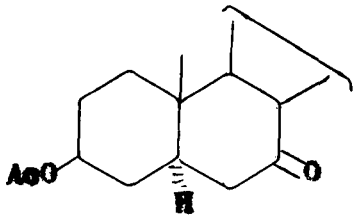
(XXIX)

ORD Spectroscopy

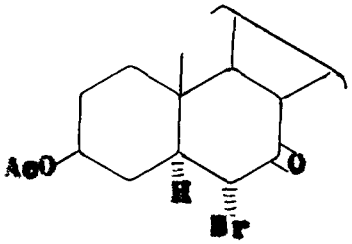
The ORD curves of steroidal ketones can be used to striking advantage in localising the position of carbonyl group and that frequently the characteristic shape of the dispersion curves would provide stereochemical information and detection of subtle conformation features of several α-brominated ketosteroid which might otherwise have to be secured by more circuitous means. Its application represents an important and powerful adjunct to steroid methodology.

The ORD curves[43] of a variety of α-halogenated steroidal ketones[44,45] have been measured and the resulting curves have been compared with those of the parent ketones[46-50]. A number of generalisations are made, the most important of which are the following; (a) Chlorine and bromine produce essentially the same effect while flourine behaves in a distinctly different fashion; (b) equatorial chlorine or bromine do not create marked dispersion changes except for minor wavelength shifts, generally toward the ultraviolet; and (c) axial chlorine or bromine leads to bathochromic shifts which can be correlated closely with the known ultraviolet changes of these chromophores; the amptitude of dispersion curve is generally increased; the sign of the cotton effect of such α-halogenated ketones can be predicted by the empirical "axial haloketone dispersion rule"[42,51-52].

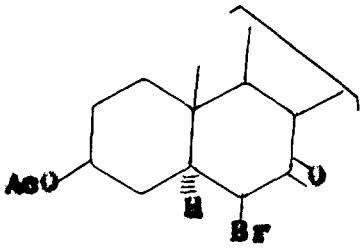
It has been seen in a variety of α-halogenated steroidal ketones that an axial halogen makes substantial change in ORD curve, may sometimes even reverse the sign of the Cotton effect, e.g.



(-ve)
(XI)



(-ve)
(XXV)

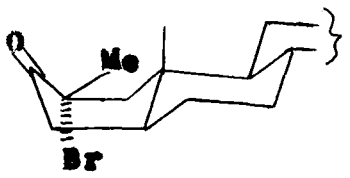


(+ve)
(XXVI)

The use of "axial α-haloketones dispersion rule"[42,51-52] provides a novel approach in determining the absolute configuration of variety of ketones[53-54]. The main points of the rule are: (a) An equatorial α-halogen causes no change, and (b) an axial halogen causes change including reversal of the sign of Cotton effect.

According to the "axial haloketone rule"[42,51-52], it would be predicted that 2β-bromo-2α-methyl-5α-cholestan-3-one (XVIII)[21,23] formulated on spectral[23,40] and chemical grounds[55,56], should exhibit a positive Cotton effect curve. In contrast to the anticipated positive Cotton effect curve, a negative one was observed, since the ORD curve is not consistent with a 2β-bromo-ketone (XVIII) nor does it permit the isomeric 2α-bromo-ketone (XVII) formulation in which A ring exists in the chair form (XX). An alternative which remains for consideration is only the boat form (XXI) of 2α-

bromo-ketone (XVII)(2α-bromine axially oriented) which shows negative Cotton effect agreeable with the prediction of "axial haloketone rule"[42,51-52]. It has been noted occasionally in the literature[57-60] that a ring may undergo a conformational change from a chair to a boat form if the proper driving force is met. This condition appears to be met in this instance, since in the chair form (XX) of 2α-bromo derivative (XVII), there is present an unfavourable diaxial methyl-methyl interaction as well as unfavourable electrostatic situation[5,9] inherent in an equatorial α-bromocyclohexanone. None of these two energetically detrimental factor is present in the boat conformation (XXI), which is in substantial agreement with predicted and found ORD curves.



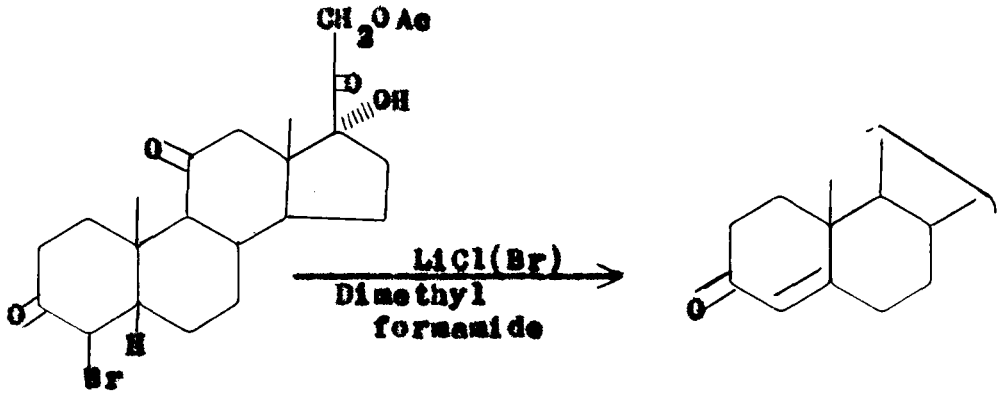
(XXI)
(Predicted-negative)
(Found-negative)

Dehydrobromination of α-brominated ketosteroids

The action of organic bases such as pyridine collidine and sodium acetate[2], etc., on α-bromoketones generally produce the corresponding unsaturated ketones in poor yields[61], but the nature

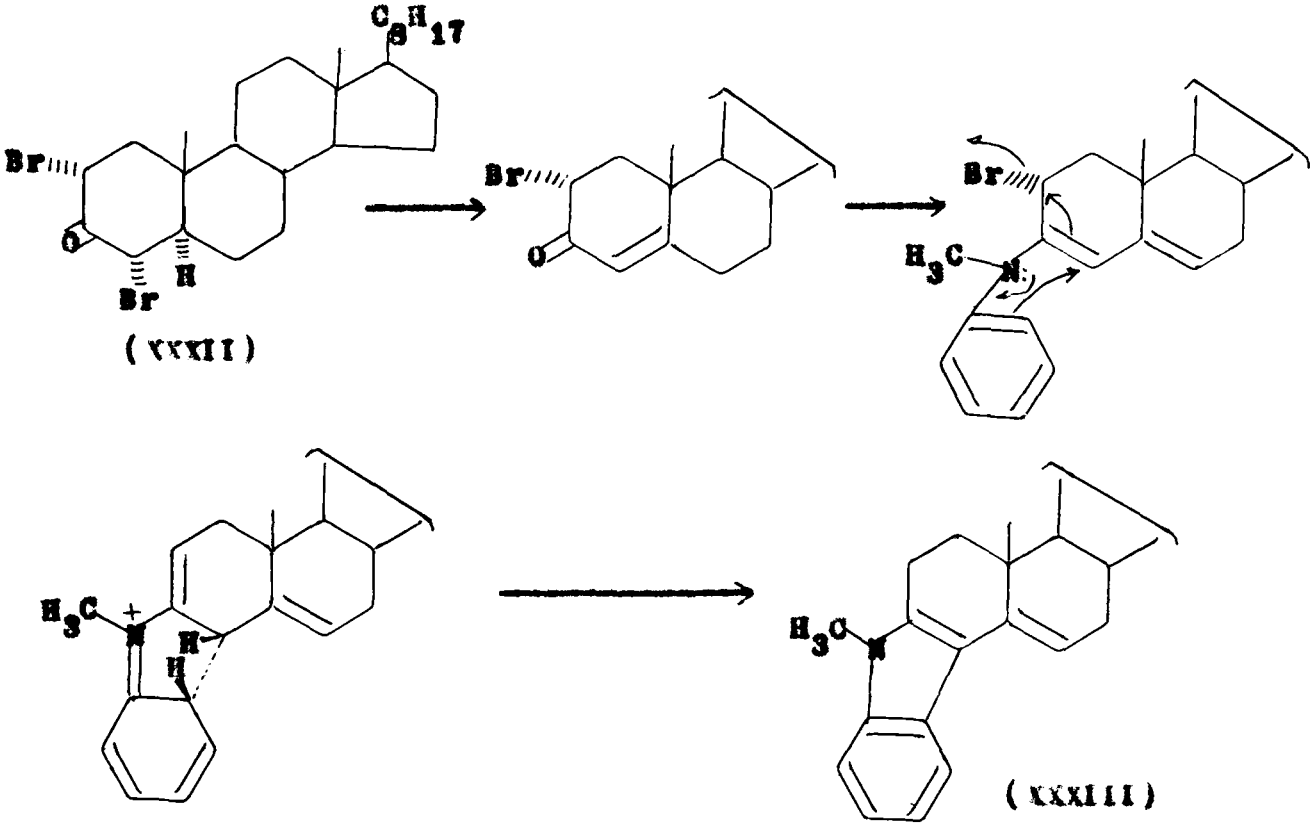
of the reagent used to remove hydrogen bromide from bromoderivatives, has considerable influence on the course of reaction. It is thus possible to obtain different reaction products from the same bromo-compound. Collidine is a useful agent because the insoluble collidine hydrobromide can be used as quantitative index for the extent of dehydrobromination. Sometimes the reaction is accompanied by rearrangement[62-64], giving rise to abnormal products.

When a mixture of 4β-bromo-17β-hydroxy-21-acetoxypregnane-3,11,20-trione (XXX)[2,65-66] and excess of lithium chloride in dimethyl formamide solution was heated under nitrogen for 5 hours at 80°, it gave cortisone acetate (XXXI).



(XXX) (XXXI)

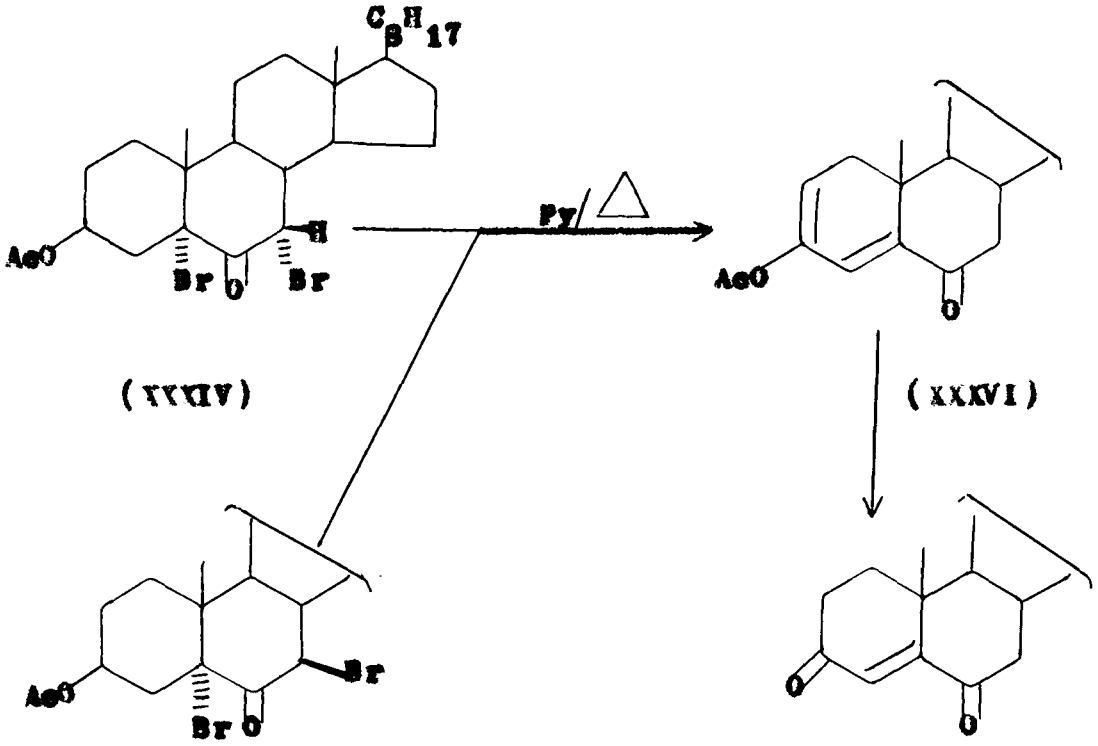
Treatment of 2α,4α-dibromocholestan-3-one (XXXII)[67-68] with N,N-dimethylaniline afforded the conjugate indole (XXXIII). The pathway by which indole (XXXIII) is formed from the (XXXII) is shown below.



(XXXII)

(XXXIII)

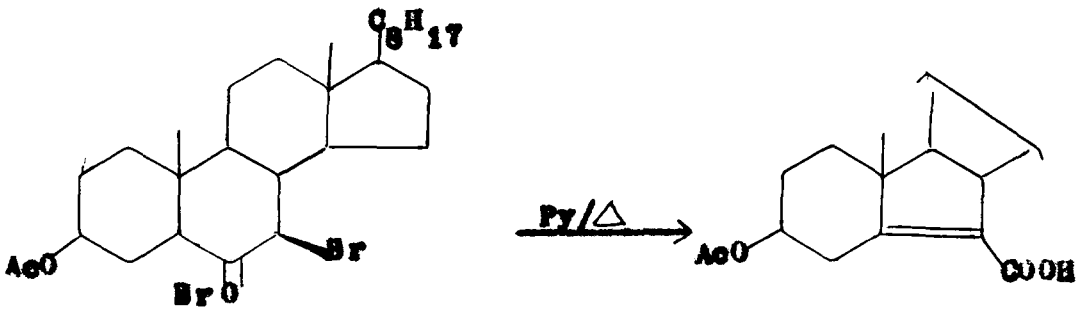
On investigating the dibromination of 6-ketocholestanyl acetate, the Heilbron group[69] isolated two isomers characterized as 3β-acetoxy-5α,7α-dibromocholestan-6-one (XXXIV) and 3β-acetoxy-5α,7β-dibromocholestan-6-one (XXXV) which on boiling pyridine yielded as the chief product, the acetoxy dienone (XXXVI) and subsequent hydrolysis of (XXXVI) gave cholest-4-ene-3,6-dione (XXXVII)[70].



(XXXIV) (XXXVI)

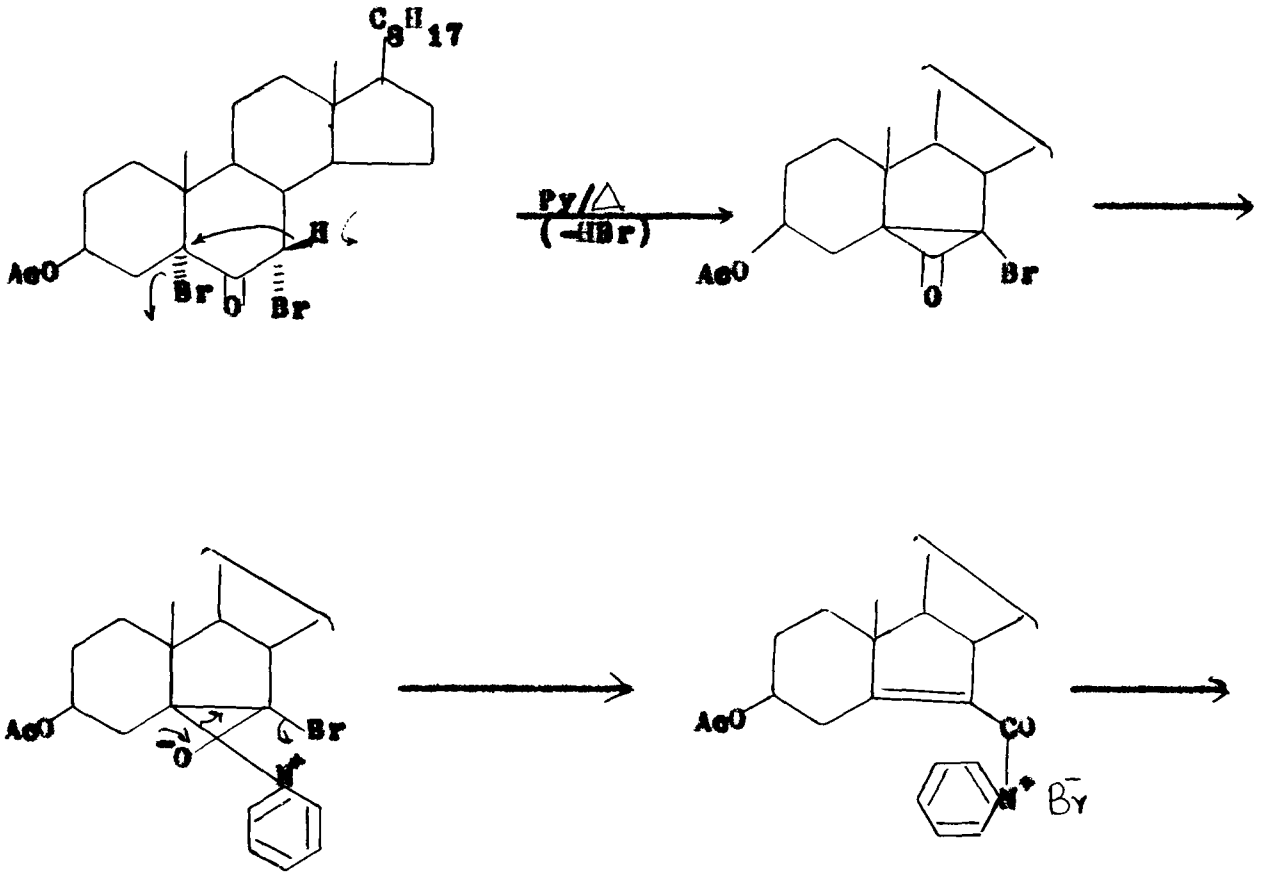
(XXXV) (XXXVII)

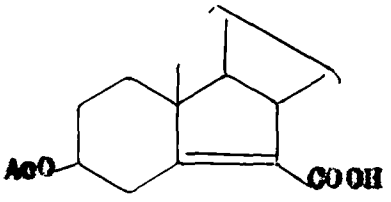
The action of boiling pyridine on 5,7-dibromo-6-ketocholestanyl acetate (XXXV)[71-74] presents a case of Favorski rearrangement in



(XXXV) (XXXVIII)

ring B proceeds with the formation of ring B contracted acid (XXXVIII). The mechanism for the formation of (XXXVIII) can be suggested as given below.





(XXXVIII)

Aromatization of steroidal compounds

The aromatization appears to be peculiar to the steroid field. Yet if the question is put-how can one ring in a polycyclic molecule be selectively aromatized-then it becomes a problem in general organic chemistry. If in addition, it is added that this selective aromatization should be accomplished in a molecule where aromatization is, in fact, blocked by the existence of quaternary carbon atoms, then the solution to this problem becomes virtually an unprecedented one in organic chemistry, especially if reasonable yields are desired.

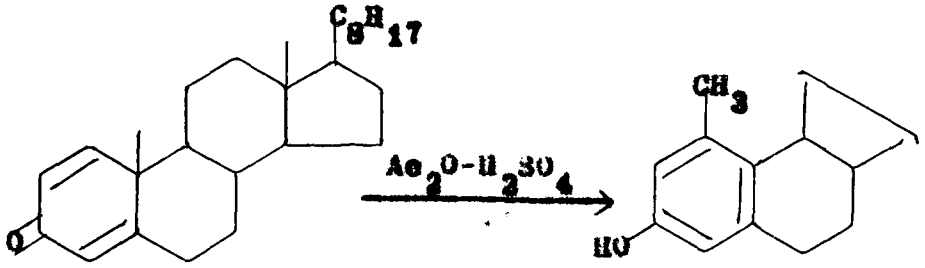
The principal approach to such a problem in organic chemistry has been dehydrogenation. While extremely valuable in structure work, it suffers from a nearly total lack of selectivity - the end product usually being a completely aromatic substance, which is often produced in poor yield. Functional groups, with the exception of lower alkyl substituents, are lost.

In the steroid field, there existed an important incentive to the solution of this problem, namely the partial synthesis of the estrogenic harmones (possessing one aromatic ring) from precursors, which contained four hydroaromatic rings and where simple aromatization was blocked by the presence of two angular methyl groups. In principle, there exist two approaches to the problem - partial aromatization with migration or with elimination of the

angular methyl group - and both of them were solved. Subsequently, ring A aromatic steroids became important starting materials in the synthesis of 19-nor-steroids by Birch reduction and it was necessary, therefore, to synthesize partially aromatic steroids with a variety of functional groups.

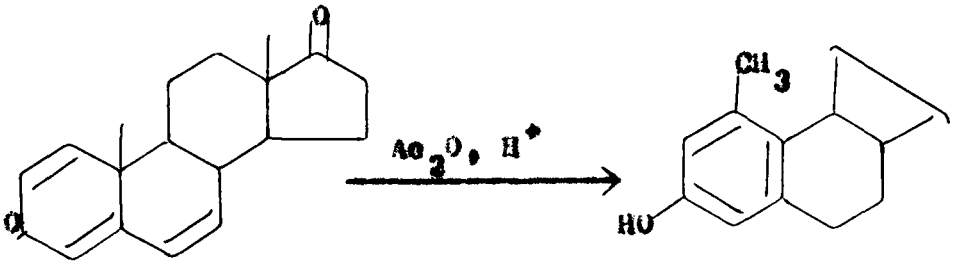
Aromatization of ring A

1,4-Cholestadiene-3-one (XXXIX)[62,75-76] by usual method (methyl migration in acetic anhydride-sulphuric acid solution subsequently termed as "dienone-phenol" rearrangement) resulted in the aromatization of ring A with the formation of 19-nor-1-methyl-3-hydroxycholesta-1,3,5(10)-triene (XL).



(XXXIX) (XL)

Application of the usual rearrangement conditions (acetic anhydride, p-toluenesulphonic acid) to androsta-1,4,6-triene-3,7-dione (XLI) yielded 19-nor-1-methyl-3-hydroxyandrosta-1,3,5(10)-6-tetraene-17-one (XLII)[77,78].

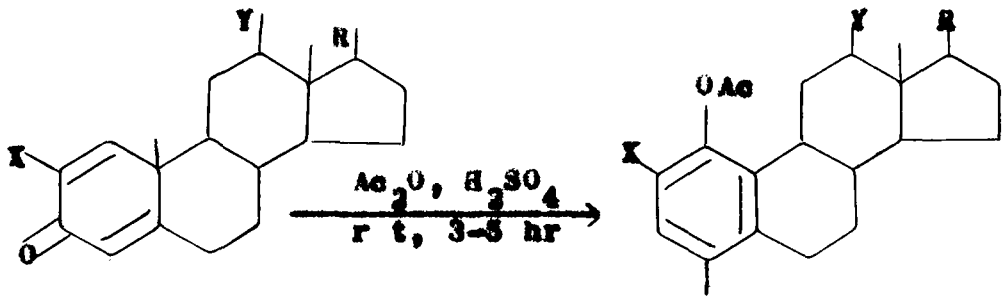


(XLI) (XLII)

The yield of the aromatised products are influenced by the presence of substituents as shown in the Table 2.

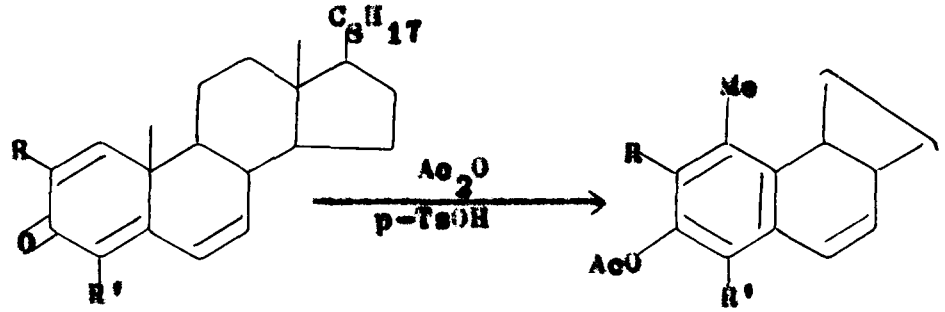
Table 2

R	X	Y	Yields(%)	Ref.
OH	H	H	40	75
OH	OMe	H	49	81
OAc	Br	H	53	82
OAc	OAc	H	86	82
C_4H_8COOMe	H	H	90	83
C_4H_8COOMe	H	OAc	85	84
C_4H_8COOMe	H	O	45	84



2-Chlorocholesta-1,4,6-triene-3-one (XLIII) and 4-chlorocholesta-1

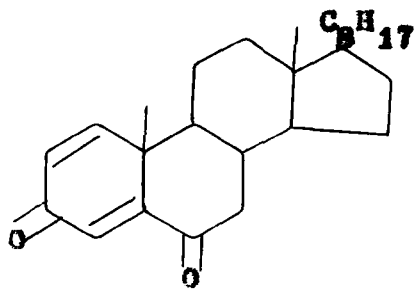
4,6-triene-3-one (XLIV)[85-88] passed smoothly into the 19-nor-3-acetoxy-2-chloro-1-methylcholesta-1,3,5(10), 6-tetraene (XLV) and 19-nor-3-acetoxy-4-chloro-1-methylcholesta-1,3,5(10),6-tetraene (XLVI), respectively when heated with acetic anhydride and p-toluenesulphonic acid.



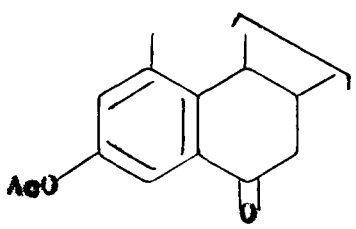
(XLIII) R=Cl, R'=H
(XLIV) R=H , R'=Cl

(XLV) R=Cl, R'=H
(XLVI) R=H , R'=Cl

Cholesta-1,4-dien-3,6-dione (XLVII)[89] when treated with acetic anhydride and p-toluenesulphonic acid furnished a product of dienone-phenol rearrangement 19-nor-3-acetoxy-1-methyl cholesta-1, 3,5(10)-trien-6-one (XLVIII).

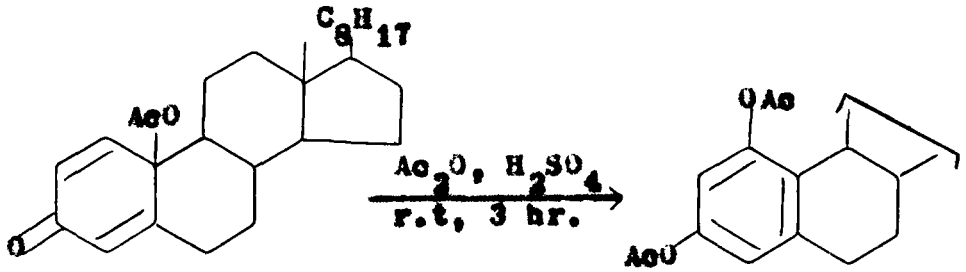


(XLVII)



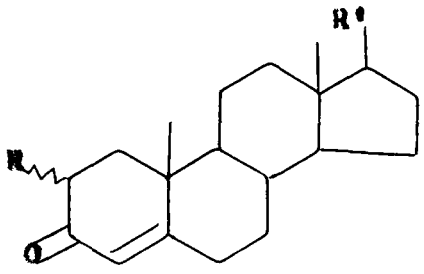
(XLVIII)

Gold and Schevenk[90] reported that compound containing 10-acetoxyl group (XLIX) underwent rearrangement with the migration of C-10 acetoxyl group to C-1, to give ring A aromatised compound (L) when treated with acetic anhydride and sulphuric acid at room temperature.

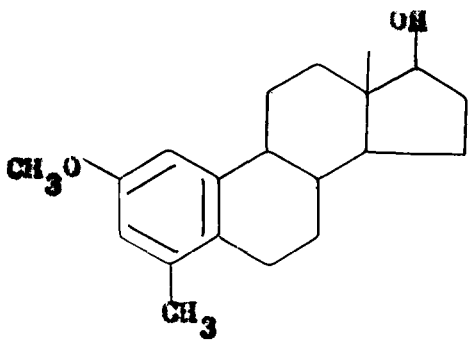


(XLIX) (L)

Clark[91] observed the rearrangement of 2α-hydroxytestosterone (LI) and the diacetate (LII), by means of p-toluenesulphonic acid in boiling methanol, to 2-methoxy-4-methylestra-1,3,5(10)-trien-17β-ol (LIII) in 23 and 10% yields, respectively.

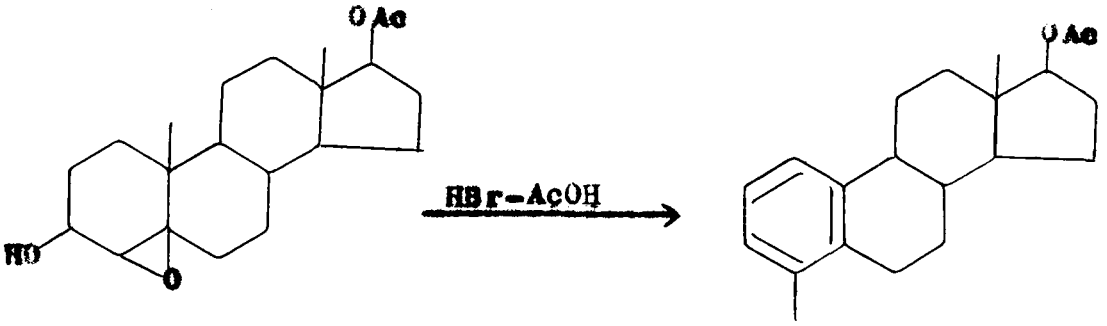


(LI) R, OH; R', OH
(LII) R=OAc; R'=OAc

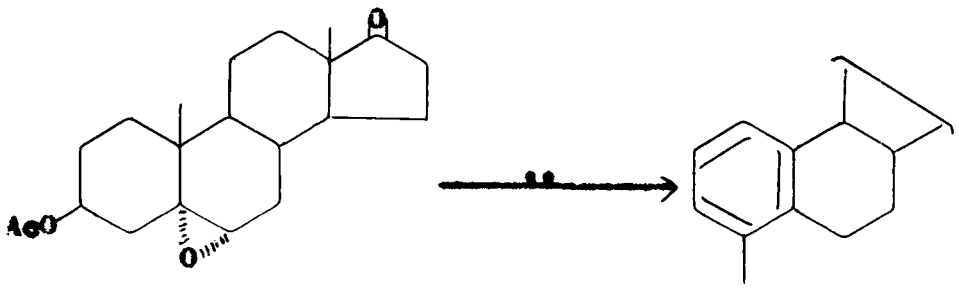


(LIII)

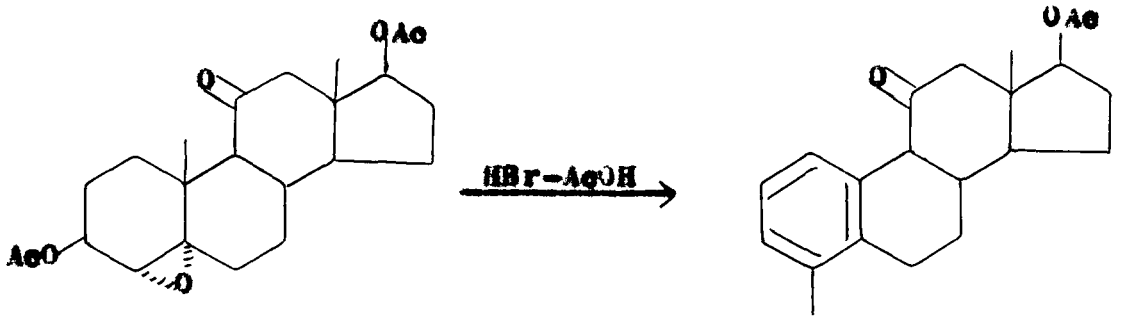
17β-Acetoxy-4β,5β-epoxyandrostan-3 -ol (LIV) and 3β-acetoxy-5α,6α-epoxyandrostan-17-one (LV)[92-95] rearrange, under the conditions of dienol-benzene rearrangement, to form 19-nor-17β-acetoxy-4-methylestra-1,3,5(10)-triene-(LVI) and 19-nor-4-methylestra-1,3,5(10)-triene-17-one (LVII), respectively. Similar rearrangement was also observed with 3β,17β-diacetoxy-4α,5α-epoxyandrostan-11-one (LVIII) which afforded 19-nor-17β-acetoxy-4-methylestra-1,3,5(10)-trien-11-one (LIX).



(LIV) (LVI)

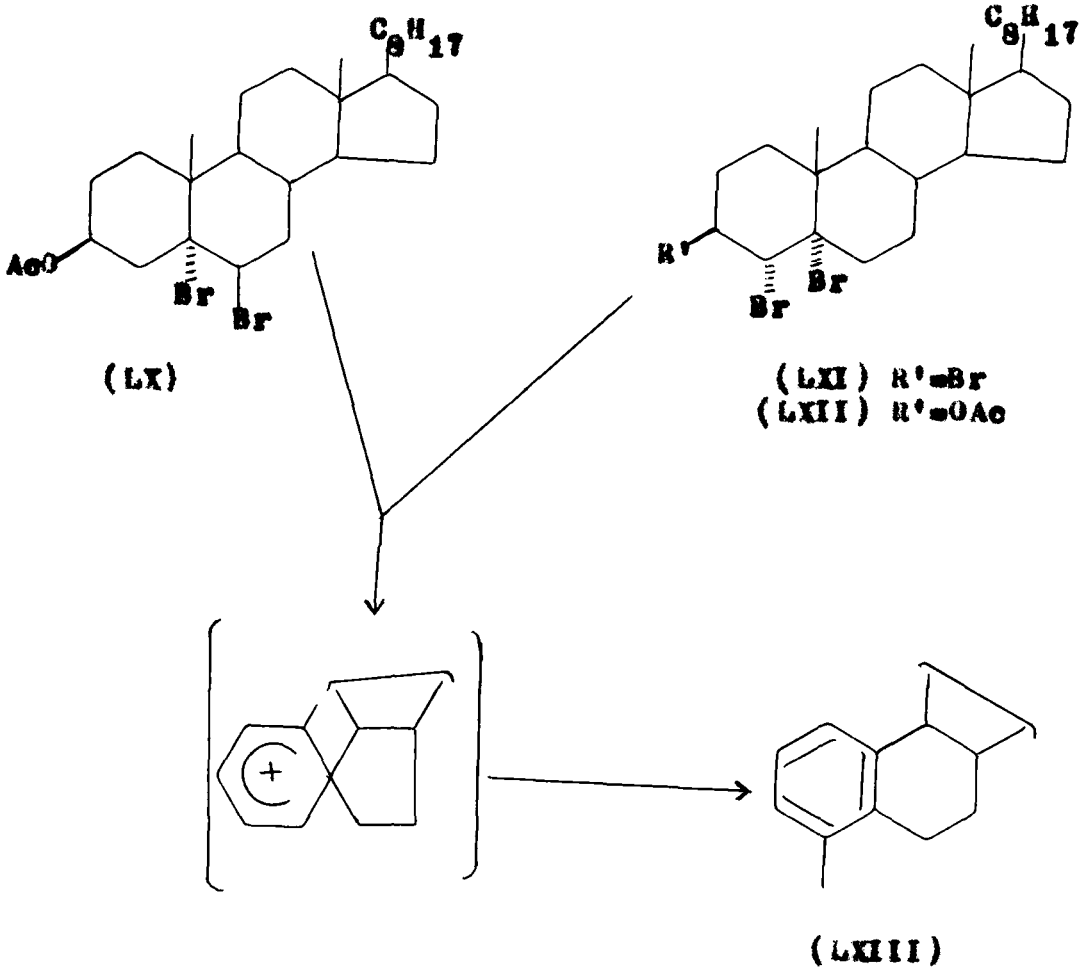


(LV) (LVII)



(LVIII) (LIX)

Steroidal compounds (LX - LXII)[94] containing three potential sites of unsaturation in rings A and B underwent aromatization into 4-methylestra-1,3,5(10)-triene (LXIII) on treatment with acetyl bromide and hydrogen bromide; under similar conditions mono and bicyclic α,β-unsaturated ketones were also aromatized.

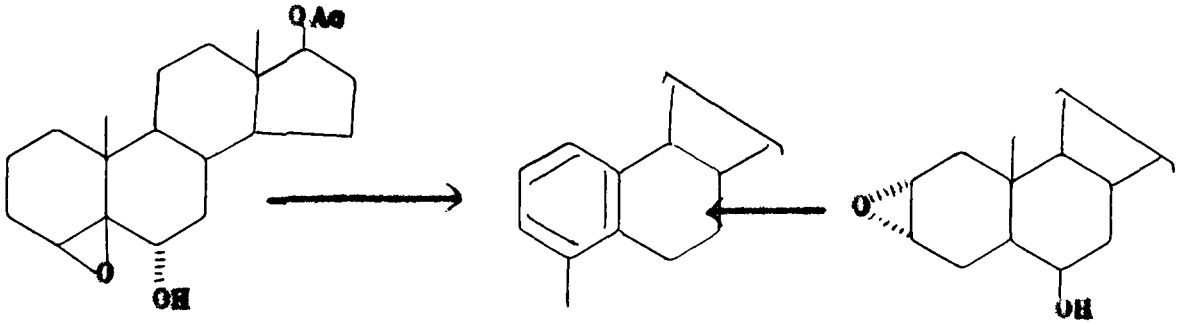


(LX)

(LXI) R'=Br
(LXII) R'=OAc

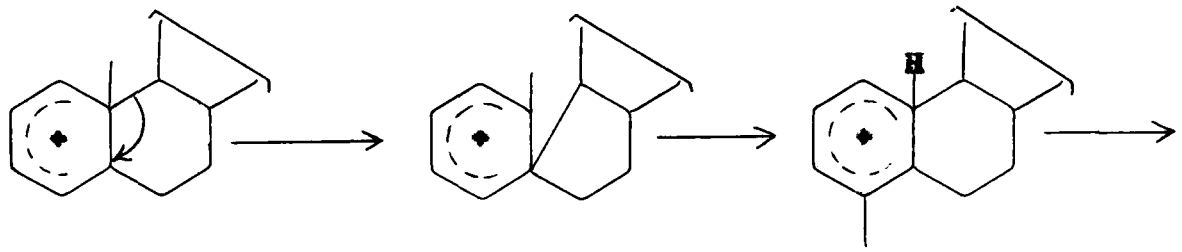
(LXIII)

Both 4β,5β-epoxy-6α-hydroxyandrostan-17β-yl acetate (LXIV) and 2α,3α-epoxy-6β-hydroxyandrostan-17β-yl acetate (LXV)[96] on treatment with refluxing hydrobromic acid in acetic acid[97], gave 4-methylestra-1,3,5(10)-trien-17β-yl acetate (LVI).

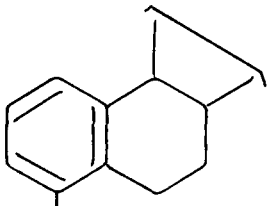


(LXIV) (LVI) (LXV)

The aromatization may proceed through a spiranic intermediate (LXVII). 4β,5β-Epoxy-6α-hydroxyandrostan-17β-yl acetate (LXIV) has an interesting disposition of functionality with regard to the formation of such an intermediate. Protonation of the epoxide, which lies trans to the migrating C(9)-C(10) bond, could initiate the formation of spiranic intermediate prior to elimination of the 6α-hydroxy group, thus trapping this double bond equivalent to ring B. Since elimination could occur after rearrangement, such a step could not preclude aromatization but would merely alter the order of events.



(LXVI) (LXVII)



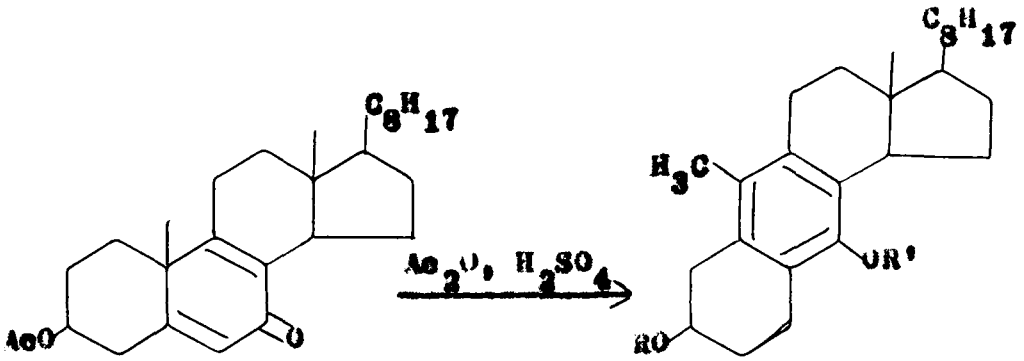
(LVI)

In the 4β,5β-epoxyhydroxy steroid, the functional groups are adjacent and one might anticipate some neighbouring group participation in the opening of epoxide ring. However, in 2∝,3∝-epoxy-6β-hydroxyandrostan-17β-yl acetate (LXV), the epoxide and hydroxy groups are separated and one cannot expect interaction between hydroxy group and epoxide. In this instance the carbonium ion (LXVI) which precedes the spiranic intermediate may be readily formed by hydrolysis of the epoxide and subsequent dehydration reactions.

Aromatisation of ring B (Anthrasteroid)

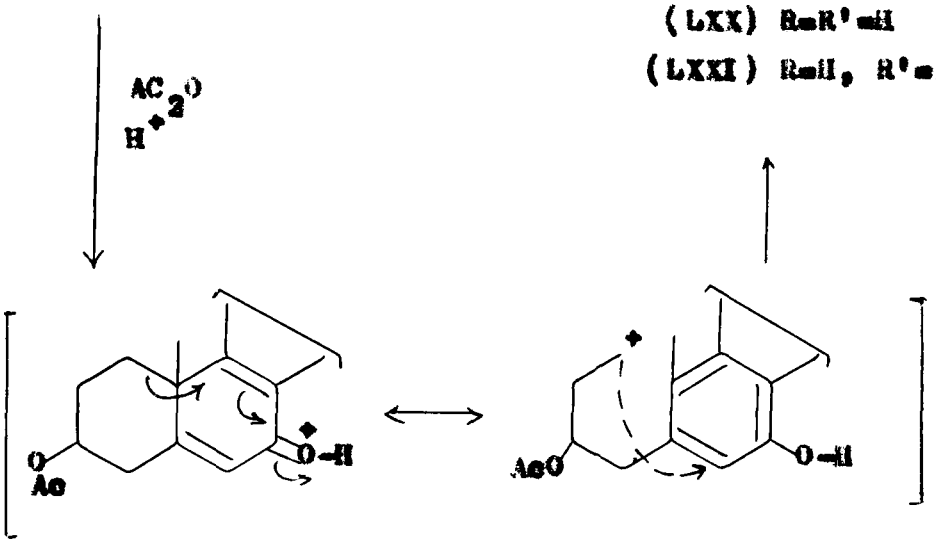
Tsuda et al.[104] carried out the dienone-phenol rearrangement of 3β-acetoxycholesta-5,8-diene-7-one (LXVIII) with acetic anhydride

and sulphuric acid to obtain a steroidal phenol of the structure (LXIX - LXXI)[105].



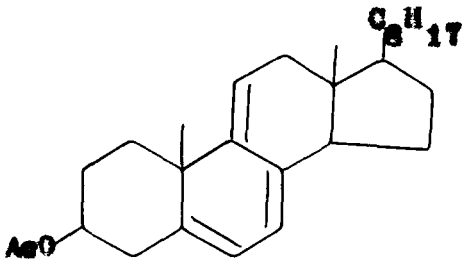
(LXVIII)

(LXIX) R=Ac, R'=H
(LXX) R=R'=H
(LXXI) R=H, R'=Ac

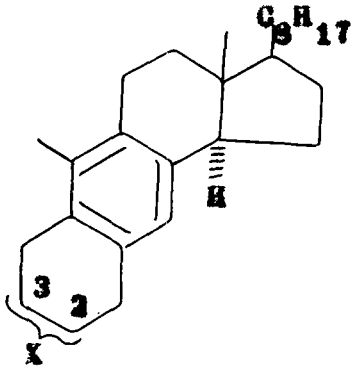


The rearrangement of cholesta-5,7,9(11)-trien-3β-yl acetate(LXXII) catalysed by p-toluenesulphonic acid leads to 14α-anthracholesta-5,7,9-trien-3β-ol (LXXIII), 14β-anthracholesta-5,7,9-trien-3β-ol (LXXIV), and anthracholesta-5,7,9,14(22)-tetraene (LXXV). The

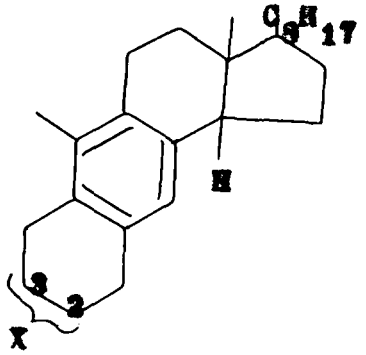
hydroxy group may be located either at position 2 or 3.



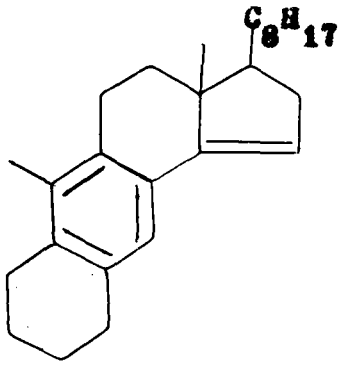
(LXXII)



(LXXIII) X=OH



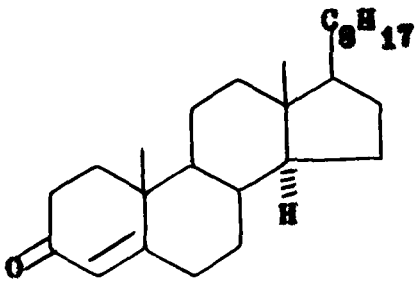
(LXXIV) X=OH



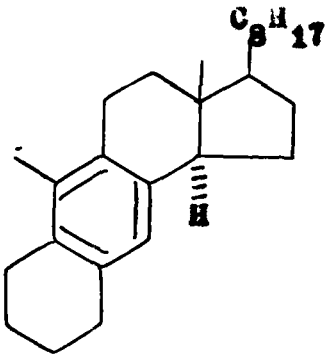
(LXXV)

Cholest-4-en-3-one (LXXVI)[111] containing three potential sites of unsaturation in rings A and B undergoes rearrangement to anthresteroid (LXXVII) on treatment with acetyl bromide and hydrogen bromide. Similar treatment of 3β,17β-diacetoxyandrost-

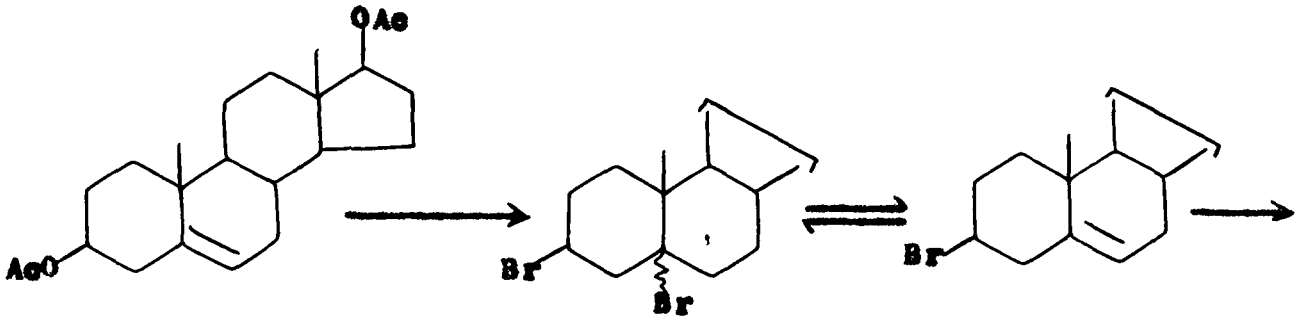
3-en (LXXVIII) having two sites of unsaturation in rings A and B, and third one in ring D gave anthrasteroid (LXXXI)[112-114].



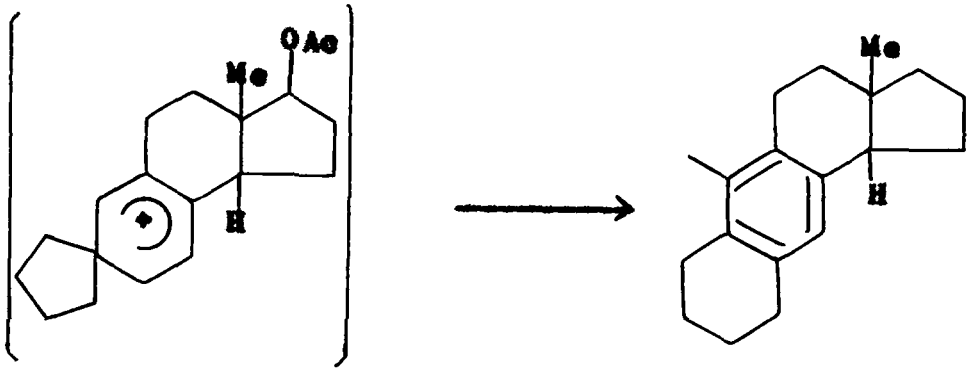
(LXXVI)



(LXXVII)

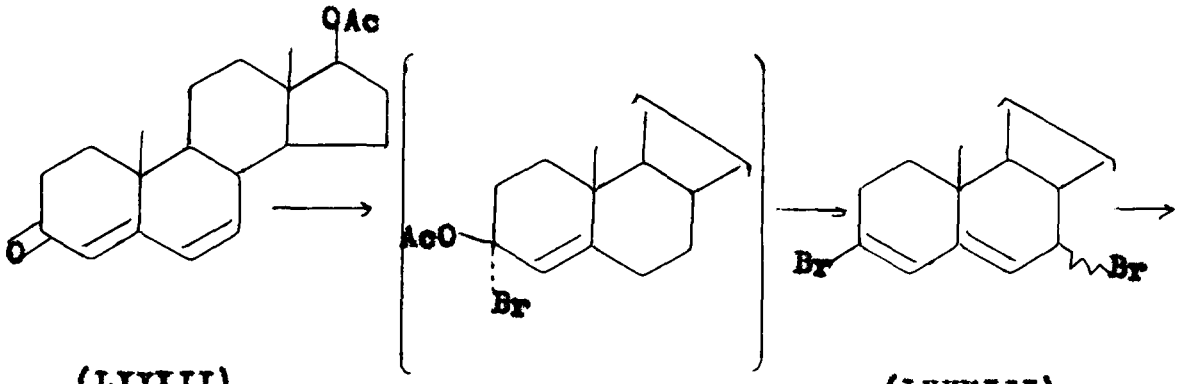


(LXXVIII) (LXXIX) (LXXX)

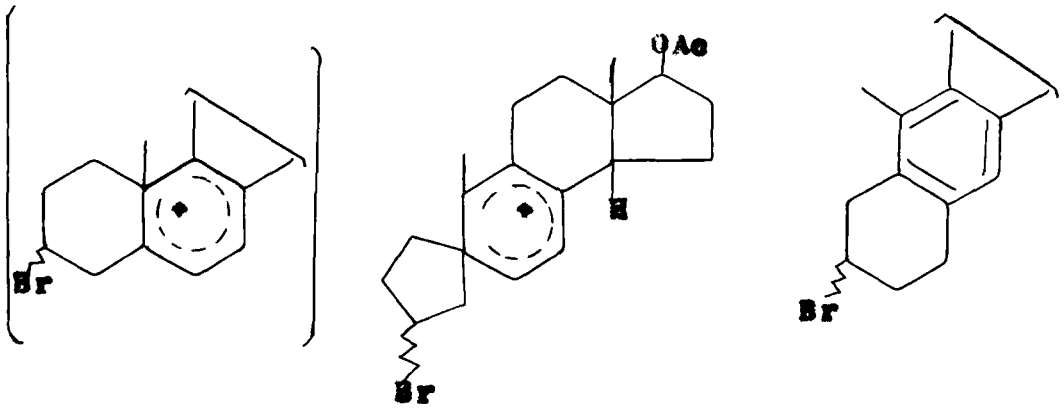


(LXXXI)

When (LXXVIII) was submitted to the above reaction conditions for shorter period, the dibromide (LXXIX) was isolated as the main product. The dibromide was readily dehydrobrominated to the monobromide (LXXX) which is probably an intermediate in the formation of the anthrasteroid (LXXXI). This transformation of monobromide to anthrasteroid involves epimerisation at C-14 followed by elimination of the 17β-acetoxy group. The resulting double bond migrates from ring D by a series of HBr additions and eliminations giving the benzonium ion having at C-14 the thermodynamically more stable β-configuration. 17β-Acetoxyandrosta-4,6-dien-3-one (LXXXII)[114,115] readily undergoes rearrangement with acetyl bromide at room temperature to anthrasteroid (LXXXIV). Treatment of the dienone (LXXXII) with acetyl bromide results in formation of the dibromodiene(LXXXIII). The dibromodiene (LXXXIII) thus formed undergoes a series of rapid eliminations and additions of hydrogen bromide, to give ring B benzonium ion which via the spiranic intermediate and by successive 1:2 shifts of C-1→C-10 bond to C-6, results in the anthrasteroid (LXXXIV).



(LXXXII) (LXXXIII)



(LXXXIV)

The epimerization at C-14 which occurs in 10-methyl and in the 19-nor series, probably proceeds through a $\Delta^{8(14)}$-olefin whose protonation will lead to the more stable C/D cis ring junction[116-120].

Mechanism

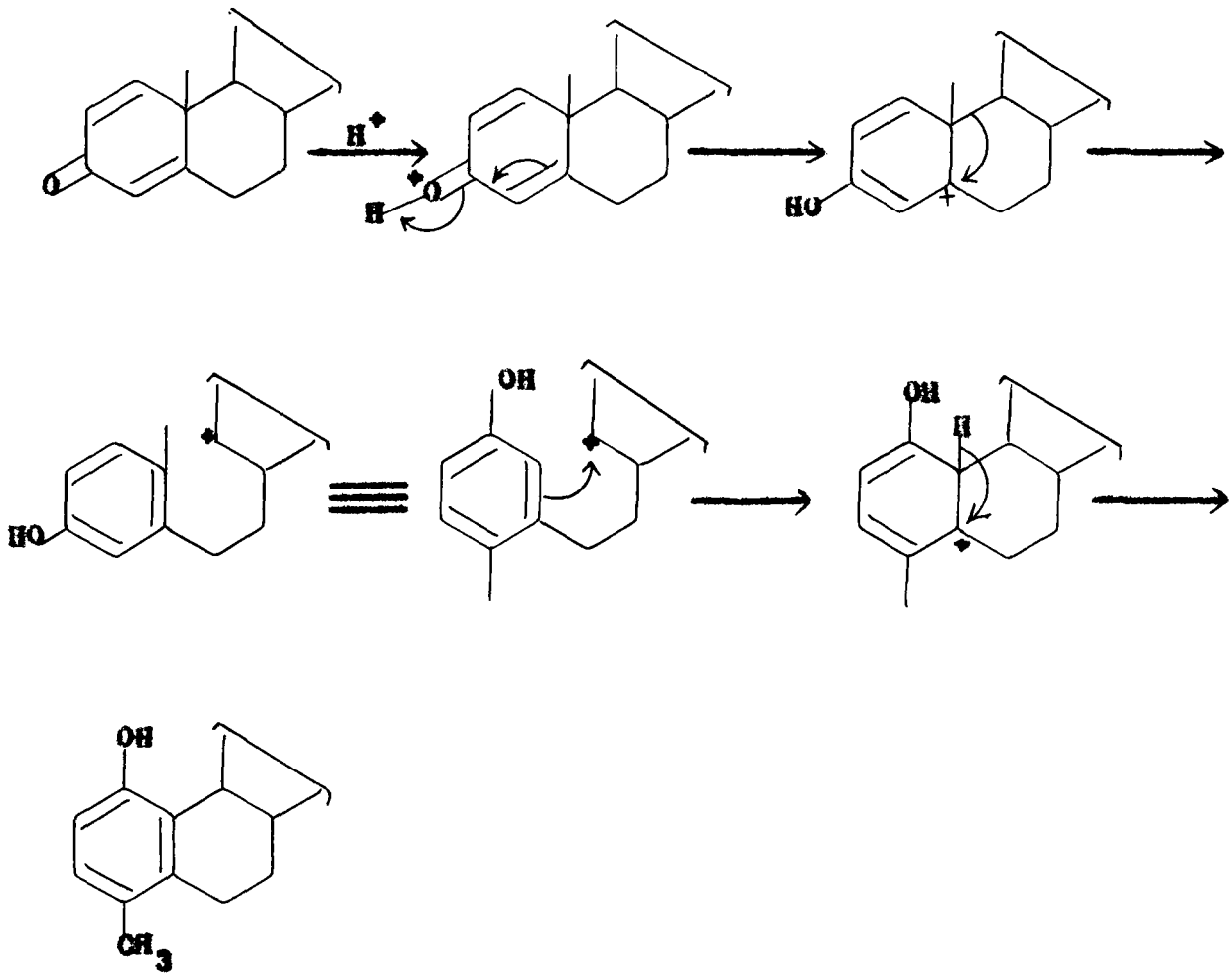
This is an area of carbonium ion chemistry which merits further examination by the physical organic chemist and as an example, there may be offered the observation that the course of the dienone-phenol rearrangement of dienones can proceed in different directions, depending upon the acid medium. No satisfactory explanation has as yet been offered, other than to imply that solvation plays an important role.

1. The Dienone-Phenol Rearrangement

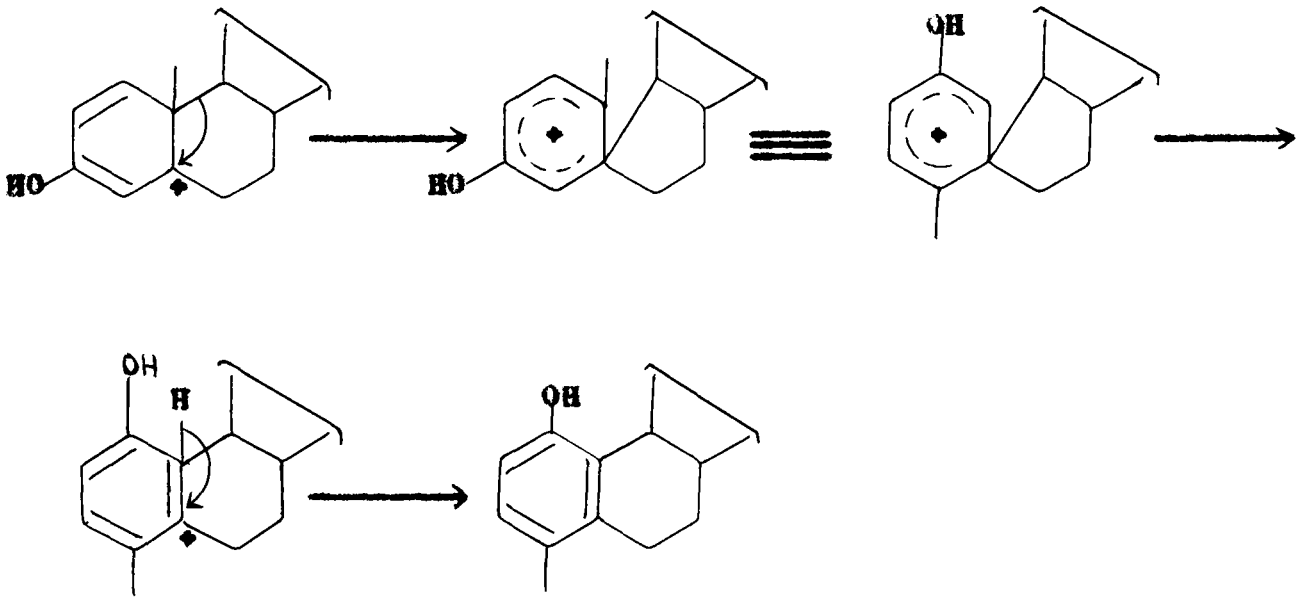
This transformation was encountered in steroid field in connection with A ring aromatization of dienone with acetic acid

and sulphuric acid. The dienone-phenol rearrangement of steroid system is controlled by internal and external factors and that methyl movement is only one mode of cleavage. Since, in general, there are two types of products resulting from the dienone-phenol rearrangement of steroids, numerous rationalisation of the exact mechanisms have been reported in an attempt to explain anomalous results. However, only three of the most generally accepted paths will be presented.

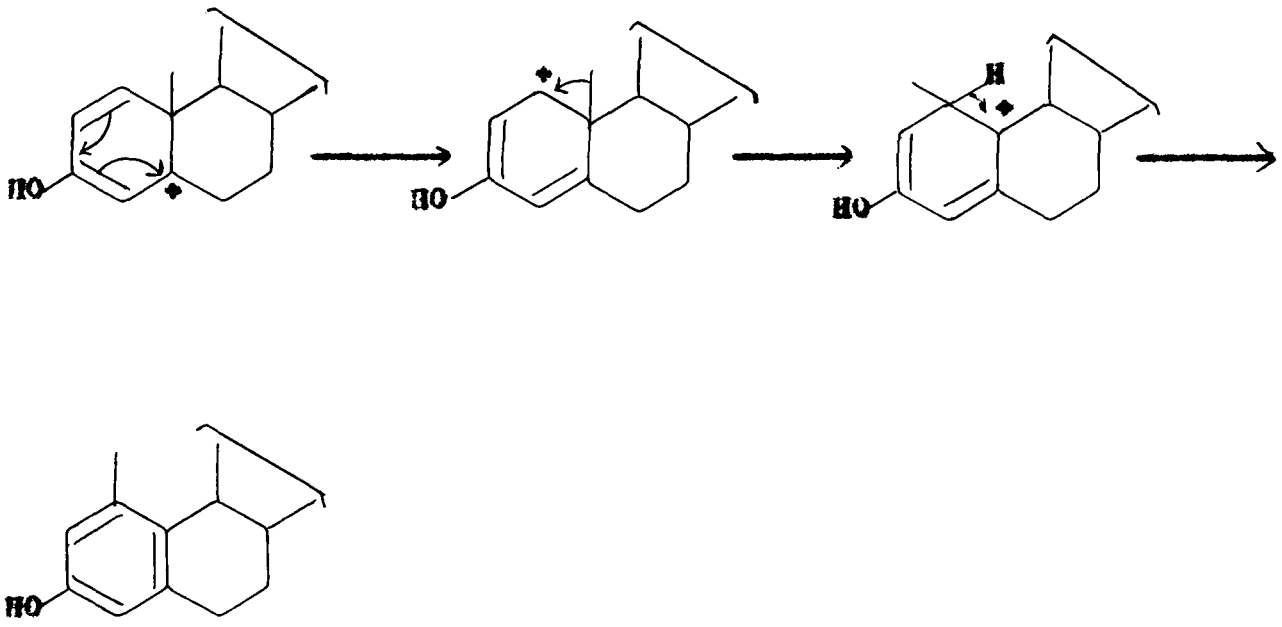
Path a



Path b



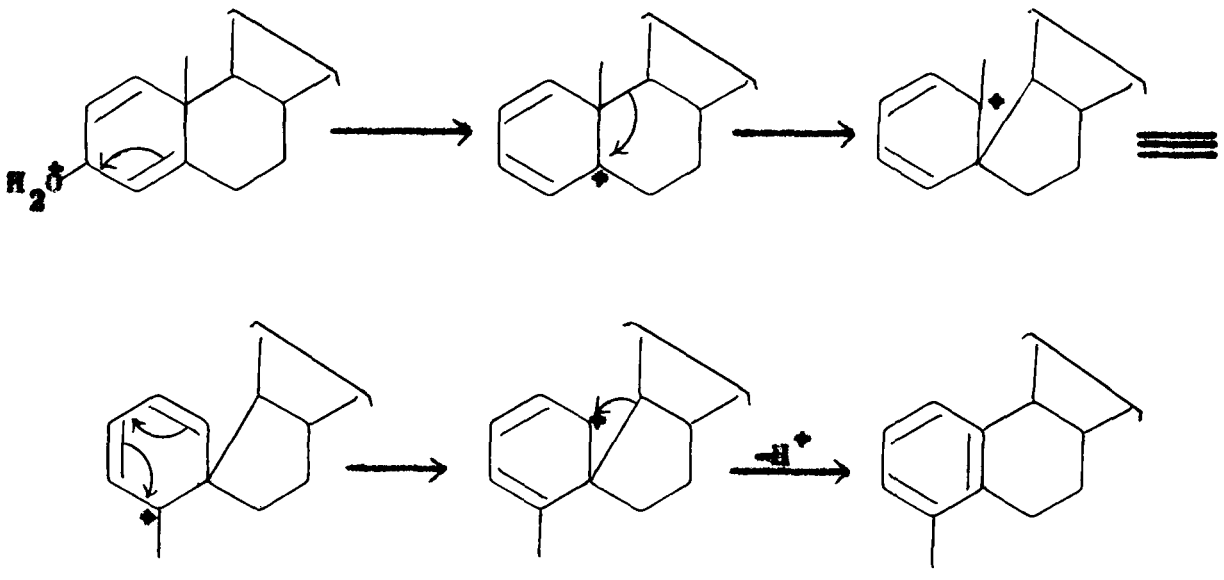
Path c



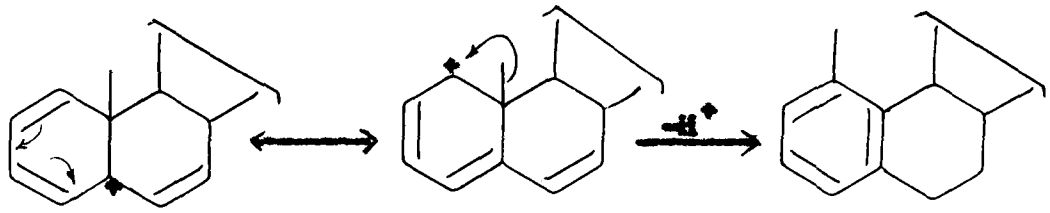
The position of the various functional groups in the steroids as well as the conditions for the reactions determine whether the phenol will be the 'para' type (path a or b) or of the 'meta' type (path c). Any functional group which tends to stabilize the positive charge on the secondary centre (C-1) in preference to that on the tertiary centre (C-5) will lead to a compound of the'meta' type, conversely, groups which have no influencing effect result in the 'para' type, via the inherently more stable tertiary cation.

The dienol-benzene Rearrangement

This rearrangement is thought to proceed through a path which is entirely analogous to that of the dienone-phenol rearrangement; the only difference is the loss of water during the incipient stages. The mechanism proceeding via the spiran intermediate is the most generally accepted one.

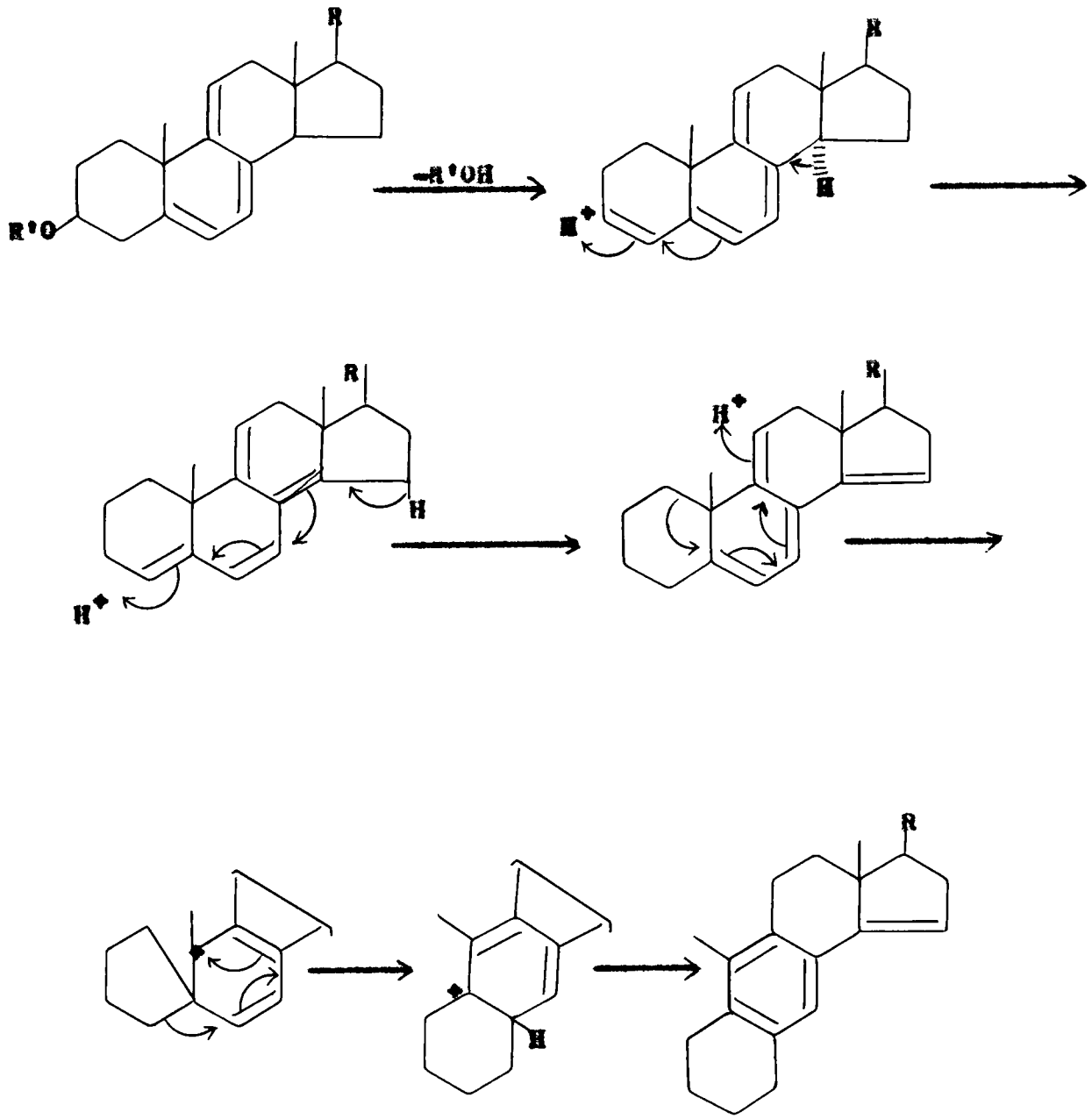


However, when Δ^6-steroid dienones are subjected to the reductive reaction conditions, the conjugation effect comes into play and the resulting product is analogous to a 'meta' type phenol.



The anthrasteroid rearrangement

This rearrangement is unique in the respect that it has as its consequence the transformation of the normal cyclopentanophenanthrenoid system to a cyclopentanoanthracenoid skeleton. The pathway by which this transformation takes place, however, is strikingly similar in nature to the dienone-phenol rearrangement. The latter, in its many instances, involves a two stage Wagner shift with B-ring contraction and expansion via a spiranic intermediate; in the anthrasteroid rearrangement, the A-ring, in essence, is correspondingly involved. The mechanism for 5,7,9(11) triene as selected is presented here. Ring-B dienones proceed by a dienone-phenol rearrangement with migration at C-1.


R
R'O
-R'OH
R
H
H
R
H
H
R
H
H

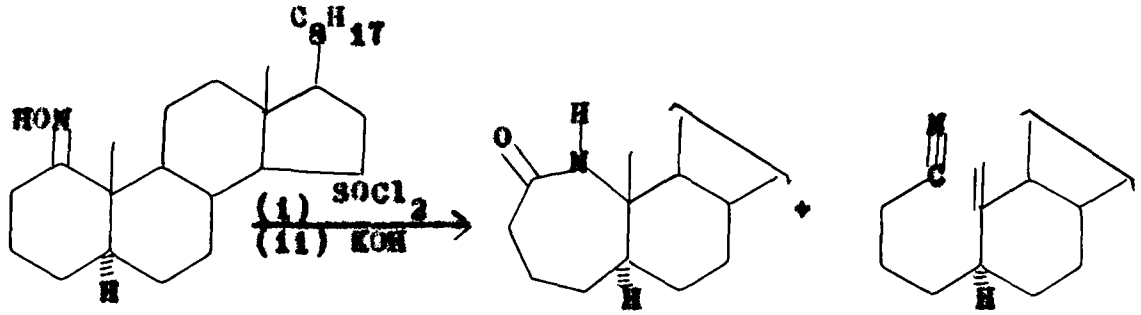
Azasteroids

The explosive growth of natural and synthetic chemistry in the field of steroids during the present century has been the result of concerted efforts of all the leading organic chemists. The problem of isolation of the steroid entities from natural sources, their great value in modern medicine and the interesting pharmacological properties have brought about an increasing interest. The synthetic modification of naturally occurring steroids, with the hope of improving pharmacological essentialities, has resulted in preparation and discovery of a number of diverse pharmacologically active, potent, highly specific commercially important therapeutic agents. The physiological activity of steroidal hormones depends on a number of factors. Among these of primary importance are stereochemistry and over all shape of the molecule. Thus, any really fundamental change (introduction of double bond, hydroxyl group and ring enlargement and contraction etc.) in the steroid nucleus should alter the stereochemistry as little as possible. Since these have involved the modification of the basic carbon skeleton of the steroid nucleus itself, it provided a opportunity to deal with many problems of fundamental organic chemistry such as mechanistic and stereochemical aspects of transformations. Moreover, the deep involvement of modern spectroscopic tools (U.v., i.r., n.m.r. and mass spectrometry) in the structural elucidation of steroidal compounds is envisaged.

Insertion of nitrogen atom into steroid nucleus has been affected mostly by the Beckmann rearrangement of steroidal ketoximes and the Schmidt reaction of steroidal ketones. A compilation of the literature on various aza steroids prepared by Beckmann rearrangement and Schmidt reaction is given by Singh et al.[121] Other methods like suitable reactions with the respective seco-keto acids, and oxasteroids, imide synthesis, Curtius and Hofmann rearrangements, total synthesis, etc. are also employed in the preparation of azasteroids. Photochemical reactions and microbiological amidations[122-126] have also been used for the preparation of different azasteroid analogues. The biological activity of azasteroids has been reviewed by Alauddin and Martin-Smith[127,128] and Martin-Smith and Sutgrue[129].

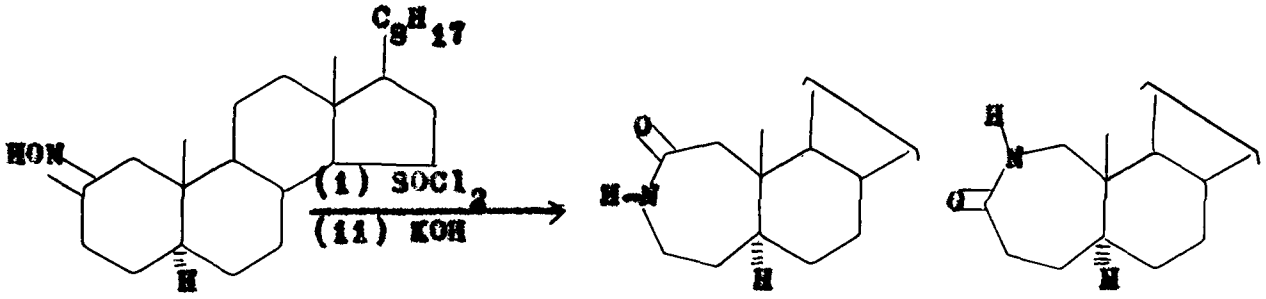
Azasteroids from saturated ketones

Shoppee et al.[130] accomplished the Beckmann rearrangement of steroidal 1- and 2-one oximes using thionyl chloride, followed by alkali treatment. 5α-Cholestan-1-one oxime (LXXXV) gives approximately equal amounts of the normal rearrangement product, 1-aza-A-homo-5α-cholestan-2-one (LXXXVI) and the abnormal "second order Beckmann" cleavage product, 1-cyano-1,10-seco-5α-cholest-10(19)-en (LXXXVII).



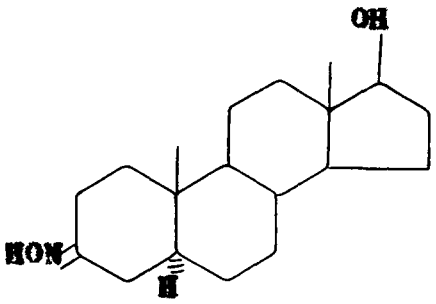
(LXXXV) (LXXXVI) (LXXXVII)

5α-Cholestan-2-one oxime (LXXXVIII) in thionyl chloride at 0°C, followed by alkali treatment furnished the isomeric lactams, 3-aza-A-homo-5α-cholestan-2-one (LXXXIX) and the 2-aza-A-homo-5α-cholestan-3-one (XC)[131].

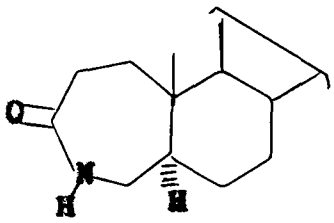


(LXXXVIII) (LXXXIX) (XC)

17β-Hydroxy-4-aza-A-homo-5α-androstan-3-one (XCII) and its isomeric lactam, 17β-hydroxy-3-aza-A-homo-5α-androstan-4-one (XCIII) were prepared from 17β-hydroxy-5α-androstan-3-one oxime (XCI)[132] under Beckmann conditions.



(XCI)



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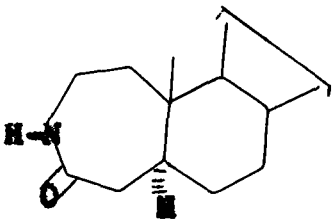
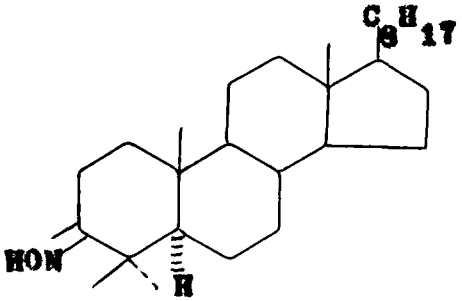
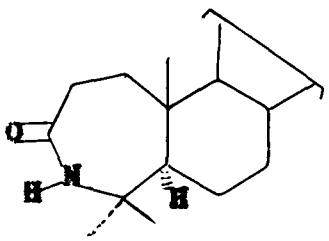
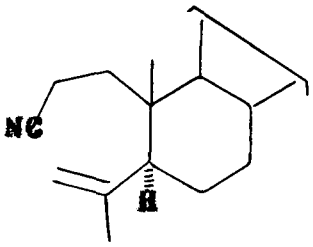


(XCII) (XCIII)

When 4,4-dimethyl-5α-cholestan-3-one oxime (XCIV) was refluxed with p-toluenesulphonyl chloride in pyridine, it gave 4-aza-A-homo-4a,4a-dimethyl-5α-cholestan-3-one (XCV) and a product of second order Beckmann rearrangement, 3-cyano-4-methyl-A-nor-3,4-seco-5α-cholest-4-en (XCVI)[133].

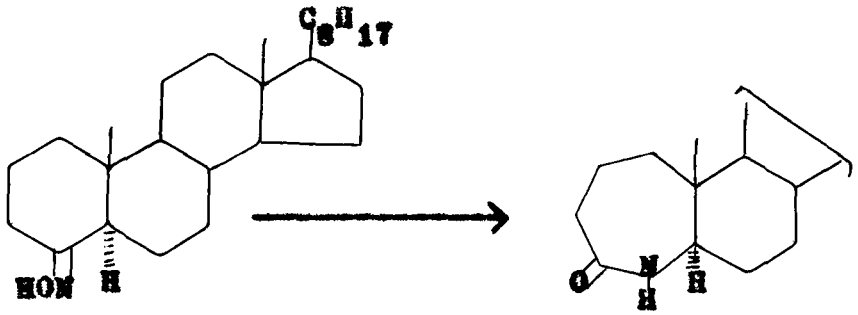






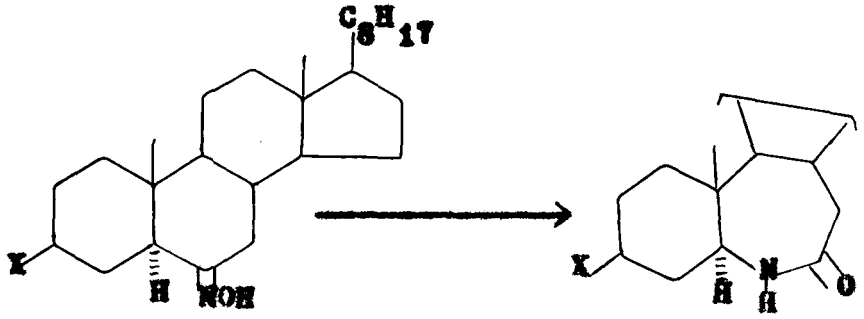
(XCIV) (XCV) (XCVII)

Treatment of 5α-cholestan-4-one oxime (XCVII) with thionyl chloride at -20° gave a single lactam, 4a-aza-A-homo-5α-cholestan-4-one (XCVIII)[130].



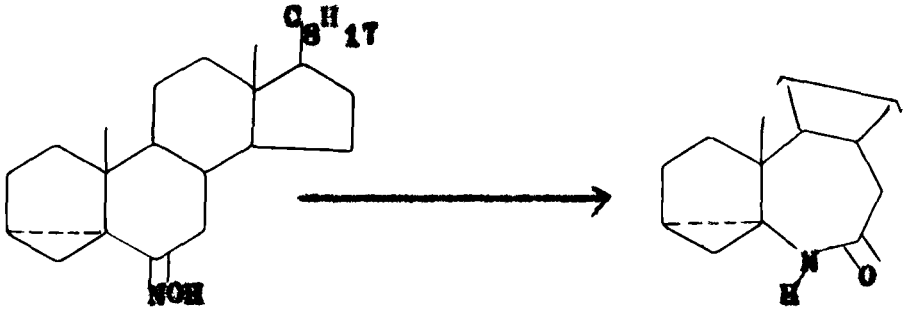
(XCVII) (XCVIII)

Ahmad et al. carried out the Beckmann rearrangement of 3β-chloro-5α-cholestan-6-one oxime (XCIX)[134] its 3β-bromo (C)[135] and 3β-iodo (CI)[136] analogues according to the method of Craig and Naik[137]. The corresponding lactams, 3β-chloro-6-aza-B-homo-5α-cholestan-7-one (CII), 3β-bromo-6-aza-B-homo-5α-cholestan-7-one (CIII), and 3β-iodo-6-aza-B-homo-5α-cholestan-7-one (CIV) were obtained.



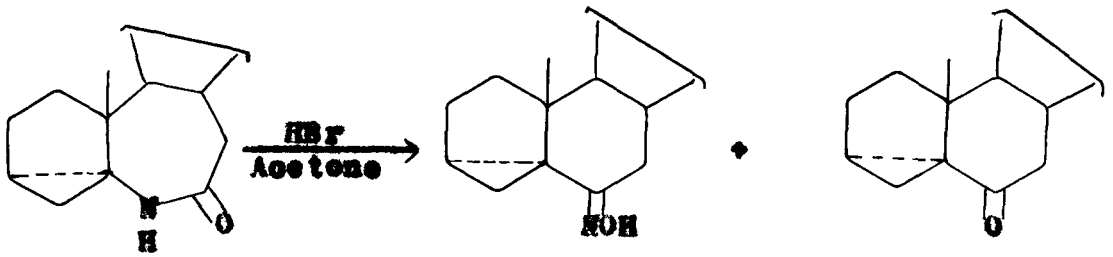
(XCIX) X = Cl (CII) X = Cl
(C) X = Br (CIII) X = Br
(CI) X = I (CIV) X = I

Ahmad et al.[135] also accomplished the Beckmann rearrangement of 3α,5-cyclo-5α-cholestan-6-one oxime (CV) which gave 6-aza-3α,5-cyclo-B-homo-5α-cholestan-7-one (CVI).

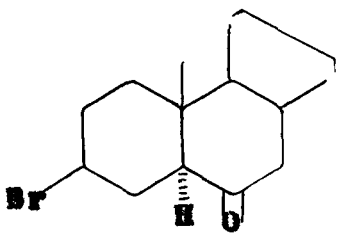


(CV) (CVI)

The lactam (CVI) has been shown to undergo 'Retro-Beckmann rearrangement', the solitary example in literature[138]. When the lactam (CVI) was treated with HBr in boiling acetone, the oxime (CV), a product of 'Retro-Beckmann rearrangement, the cycloketone (CVII), the hydrolysed product of the oxime (CV) and the bromo-ketone (CVIII), an artefact of the cycloketone (CVII) were obtained.

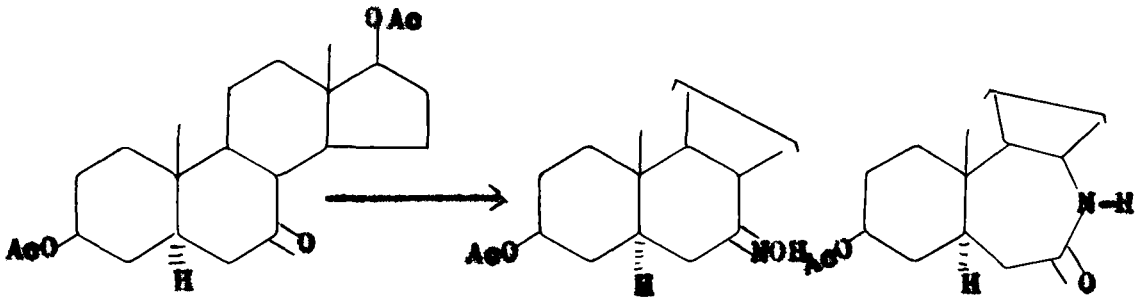


(CVI) (CV) (CVII)



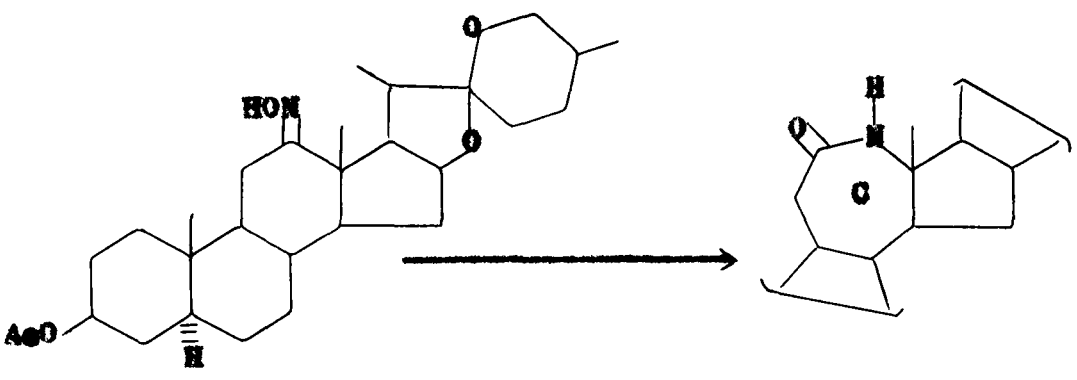
(CVIII)

The Schmidt reaction of 3β,17β-diacetoxy-5α-androstan-7-one (CIX)[139] afforded a single lactam, 3β,17β-diacetoxy-7a-aza-B-homo-5α-androstan-7-one (CXI). The same lactam (CXI) was also prepared from 3β,17β-diacetoxy-5α-androstan-7-one oxime (CX) through Beckmann rearrangement.



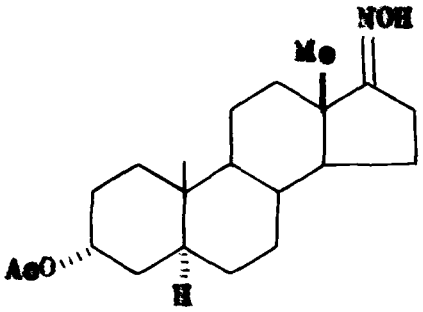
(CIX) (CX) (CXI)

Masur[140] observed that hecogenin acetate oxime (CXII) on heating with p-toluenesulphonyl chloride at 100° provided 3β-acetoxy-12a-aza-C-homo-5α-, 22α-spirostan-12-one (CXIII).

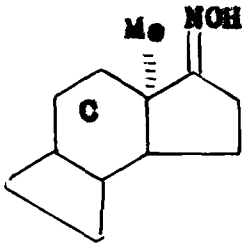


(CXII) (CXIII)

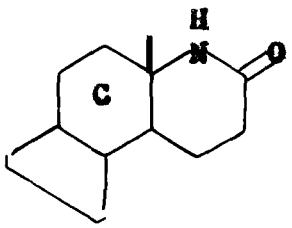
Suginome and coworkers[141] reported the photo-induced transformation of 3α-acetoxy-5α-androstan-17-one oxime (CXIV) and its 13α-isomer (CXV) to lactams, 3α-acetoxy-17a-aza-D-homo-5α-androstan-17-one (CXVI) and 3α-acetoxy-13α-methyl-17a-aza-D-homo-5α-androstan-17-one (CXVII), respectively.



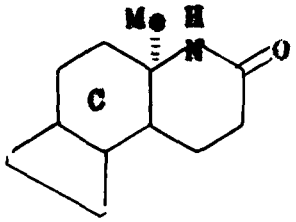
(CXIV)



(CXV)

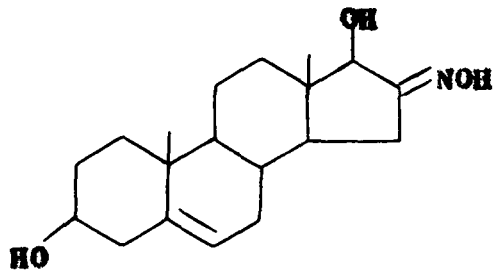


(CXVI)

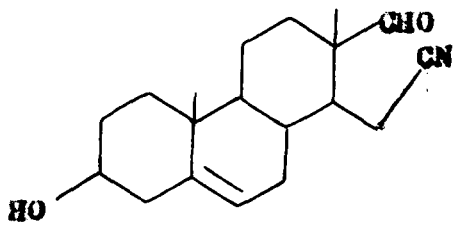


(CXVII)

The Beckmann fragmentation reaction of 3β,17β-dihydroxy-16-oximinoandrost-5-ene (CXVIII)[142] gave 3β-hydroxy-16,17-seco-17-formylandrost-5-en-16-nitrile (CXIX).



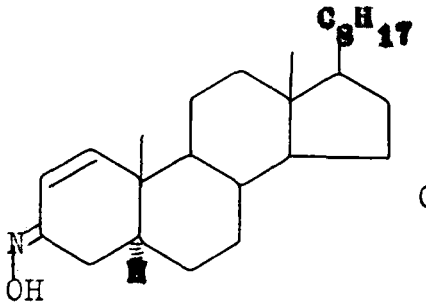
(CXVIII)



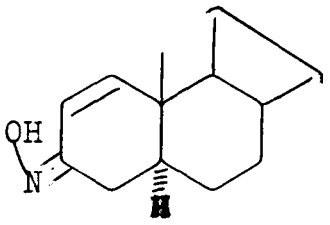
(CXIX)

Azasteroids from α,β-unsaturated ketones

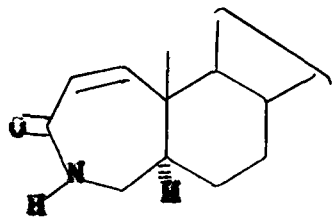
5α-Cholest-1-en-3-one oxime (CXX)[143] which is an anti-isomer, does not undergo the Beckmann rearrangement with thionyl chloride at 20°. The syn-oxime (CXXI) of the mixture of the isomeric oximes, under same reaction conditions, gives the lactam, 4-aza-A-homo-5α-cholest-1-en-3-one (CXXII).



(CXX)

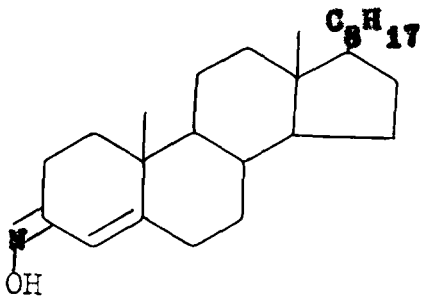


(CXXI)

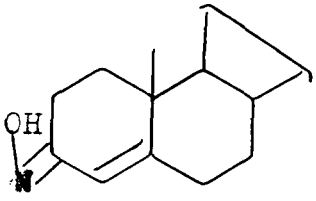


(CXXII)

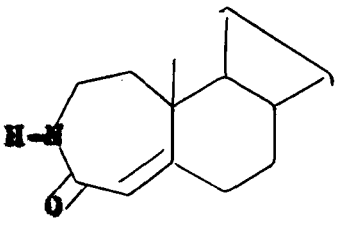
Shoppee et al.[131,144] reported the Beckman rearrangement of cholest-4-en-3-one oxime (syn-form)(CXXIII) which gave 3-aza-A-homo-cholest-4a-en-4-one (CXXV). The anti-form (CXXIV) failed to undergo rearrangement.



(Syn-form)
(CXXIII)

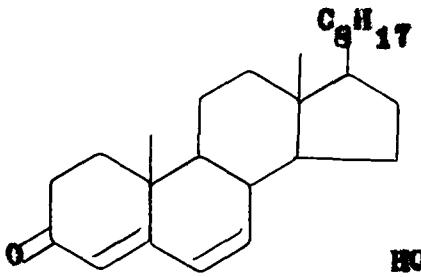


(Anti-form)
(CXXIV)

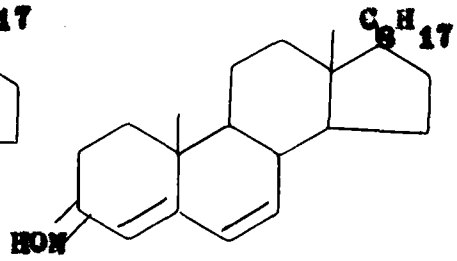


(CXXV)

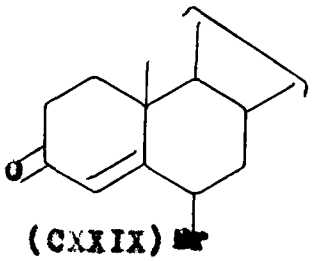
Ahmad et al.[145] reported the Schmidt reaction of cholesta-4, 6-dien-3-one (CXXVI) and the Beckmann rearrangement of the corresponding oxime (CXXVII). They obtained the same lactam, 3-aza-A-homocholesta-4a,6-dien-4-one (CXXVIII) in both the cases. The same lactam (CXXVIII) was obtained from the Schmidt reaction of 6β-bromocholest-4-en-3-one (CXXIX). The ketone (CXXIX) also provided the oxime (CXXVII); obviously dehydrobromination has occurred under the reaction conditions.



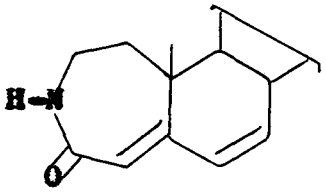
(CXXVI)



(CXXVII)

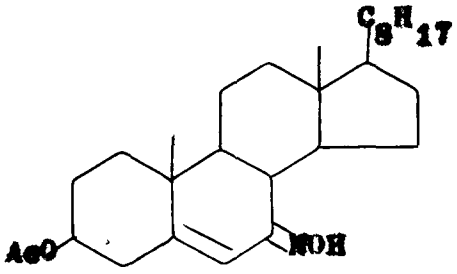


(CXXIX)

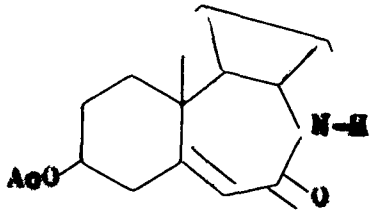


(CXXVIII)

3β-Acetoxycholest-5-en-7-one oxime (CXXX) on Beckmann rearrangement with p-toluenesulphonyl chloride and pyridine gave 3β-acetoxy-7a-aza-B-homocholest-5-en-7-one (CXXXI)[146,147].

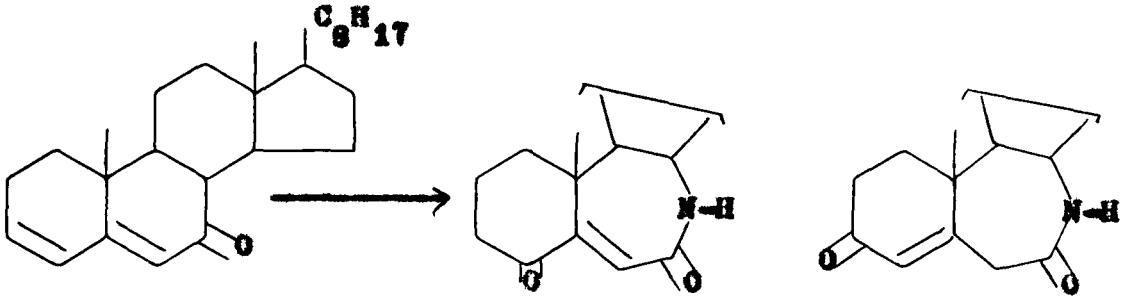


(CXXX)



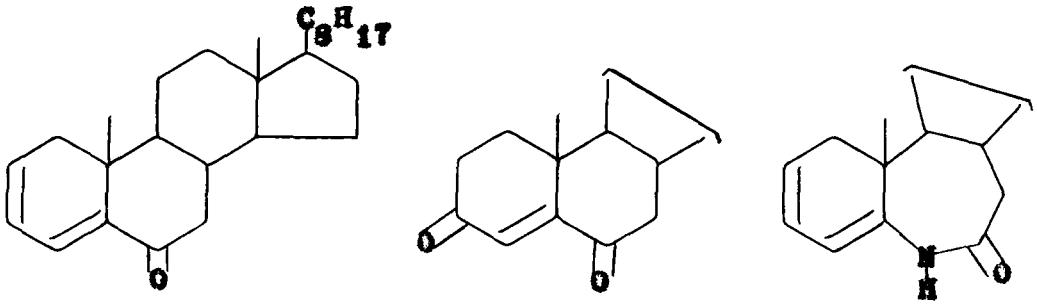
(CXXXI)

The Schmidt reaction of cholesta-3,5-dien-7-one (CXXXII)[148-149] was examined using three molar equivalents of sodium azide, and it gave 7a-aza-8-homocholest-5-ene-4,7-dione (CXXXIII) and the alternative product, 7a-aza-8-homocholest-4-ene-3,7-dione(CXXXIV).

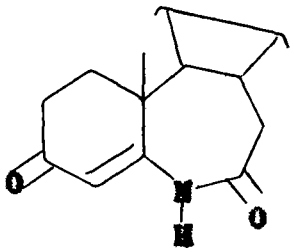


(CXXXII) (CXXXIII) (CXXXIV)

Cholesta-2,4-dien-6-one (CXXXV)[150] on treatment with sodium azide (1 mole) and polyphosphoric acid afforded three products which were identified as cholest-4-ene-3,6-dione (CXXXVI), 6-aza-8-homocholesta-2,4-dien-7-one (CXXXVII), the product of normal Schmidt reaction and 6-aza-8-homocholest-4-ene-3,7-dione (CXXXVIII).



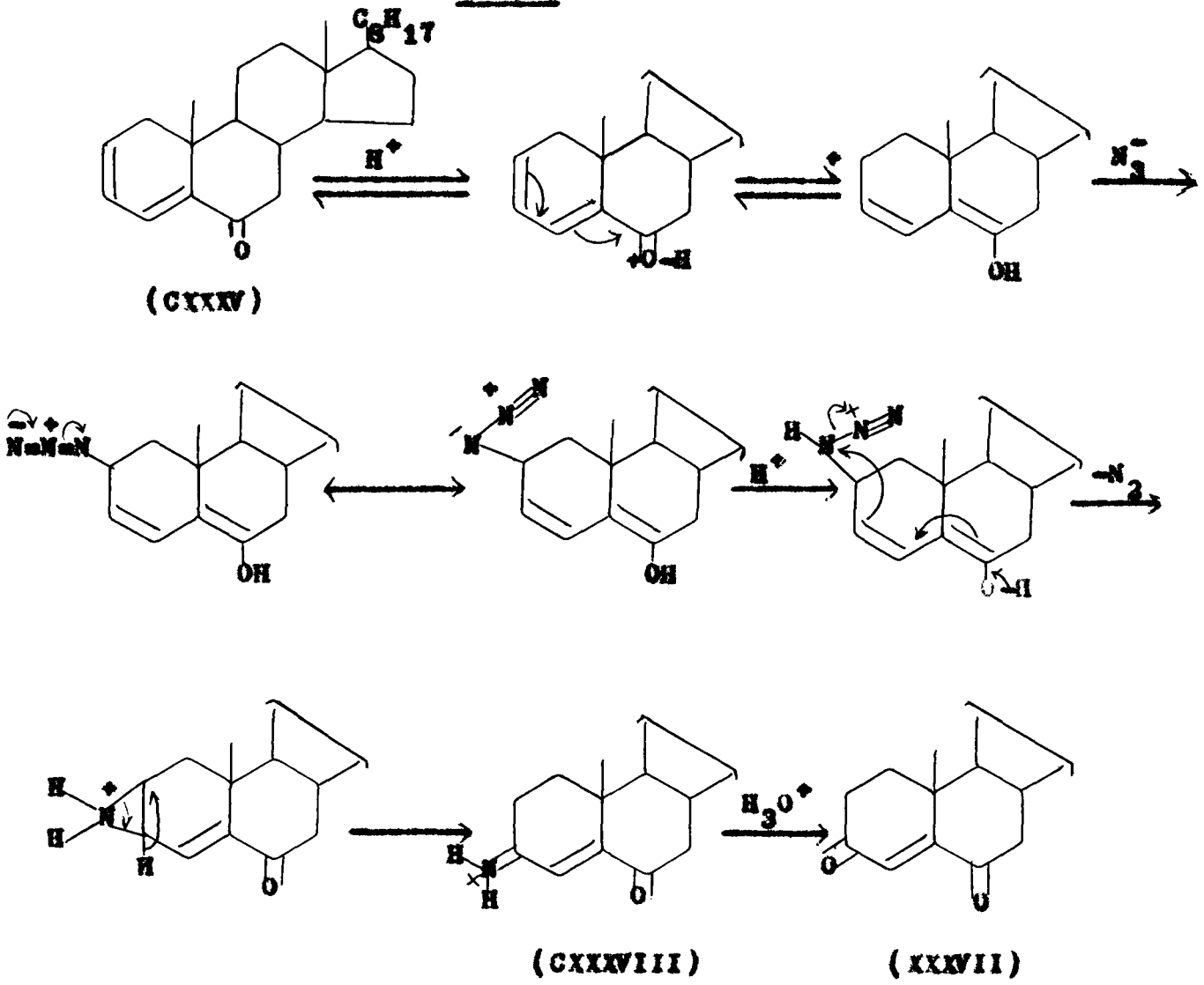
(CXXXV) (XXXVII) (CXXXVI)



(CXXXVII)

The formation of cholest-4-ene-3,6-dione (XXXVII) from (CXXXV) may be shown to occur according to the scheme given below[148].

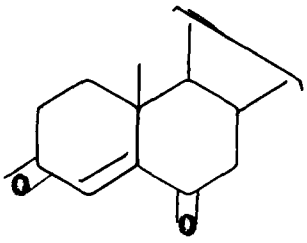
Scheme



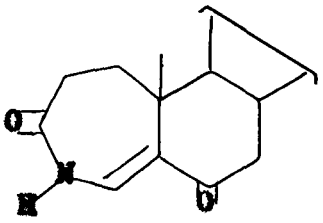
(CXXXV)

(CXXXVIII) (XXXVII)

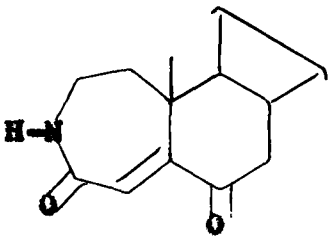
It was shown that (XXXVII) is not the precursor of the lactam (CXXXVII) since Schmidt reaction of the former[151] provided 4-aza-A-homocholest-4a-ene-3,6-dione (CXXXIX), 8-aza-A-homocholest-4a-ene-4,6-dione (CXL) and the dilactam, 4,6-diaza-A,B-bishomocholest-4a-ene-3,7-dione (CXLI).



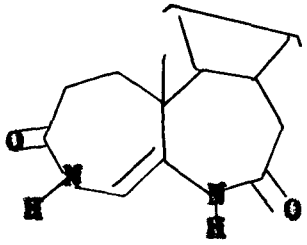
(XXXVII)



(CXXXIX)

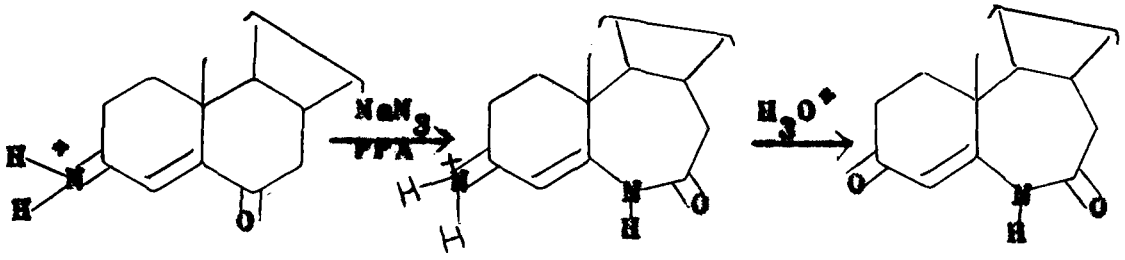


(CXL)



(CXLI)

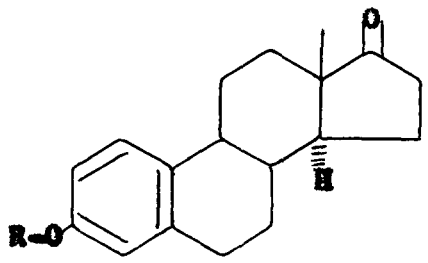
With this observation they suggested that the precursor of the keto-lactam (CXXXVII) could be the imino intermediate (CXXXVIII), which on normal Schmidt reaction followed by acid hydrolysis gives (CXXXVII).



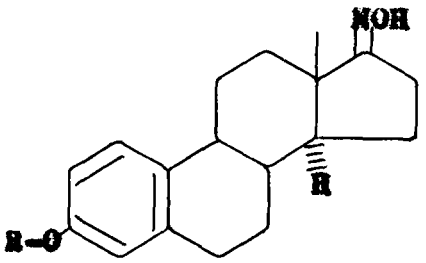
(CXXXVIII)

(CXXXVII)

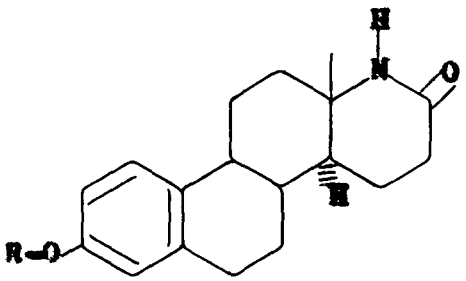
Bela and coworkers[152] obtained a lactam, 3—hydroxy-1 - aza-D-homoestra-1,3,5(10)-trien-17-one (CXLVIII) accompanied with second type of Beckmann product (CLI), when 3-hydroxyestra-1,3,5(10)-trien-17-one oxime (CXLV) was heated in pyridine containing 4-AcNH $C_6H_4SO_2Cl$. 3—Acetoxy estra-1,3,5(10)-trien-17-one oxime (CXLVI) and 3—methoxyestra-1,3,5(10)-trien-17-one oxime (CXLVII) gave corresponding azasteroids (CXLIX,CL) and second kind of Beckmann products (CLII,CLIII).



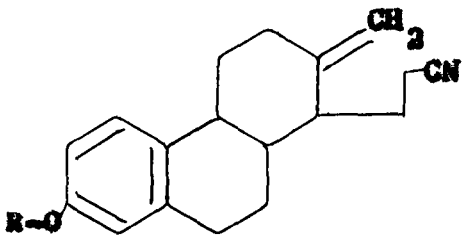
(CXLII) R=H
(CXLIII) R=Ac
(CXLIV) R=Me



(CXLV) R=H
(CXLVI) R=Ac
(CXLVII) R=Me



(CXLVIII) R=H
(CXLIX) R=Ac
(CL) R=Me

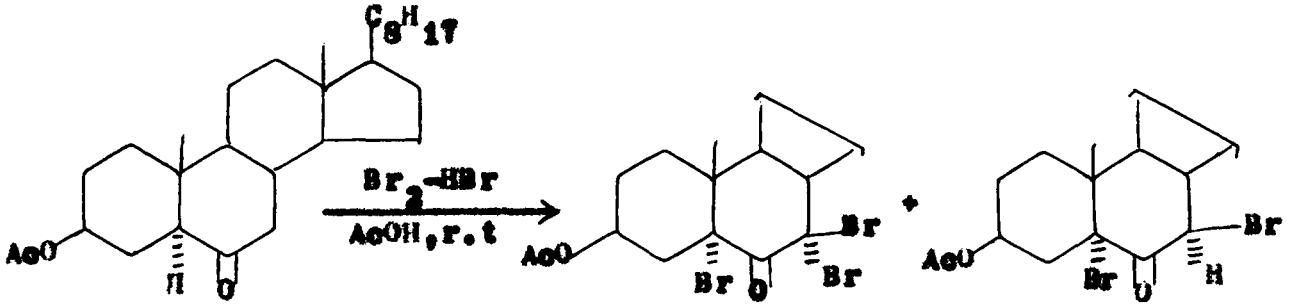


(CLI) R=H
(CLII) R=Ac
(CLIII) R=Me

They also reported the formation of same lactams, 3-hydroxy-17a-aza-D-homoestra-1,3,5(10)-trien-17-one (CXLVIII), 3-acetoxy-17a-aza-D-homoestra,1,3,5(10)-trien-17-one (CXLIX), and 3-methoxy-18-aza-D-homoestra-1,3,5(10)-trien-17-one (CL), when 3-hydroxyestra-1,3,5(10)-trien-17-one (CXLII), 3-acetoxyestra-1,3,5(10)-trien-17-one (CXLIII) and 3-methoxyestra-1,3,5(10)-trien-17-one (CXLIV) were heated in polyphosphoric acid and sodium azide, respectively.

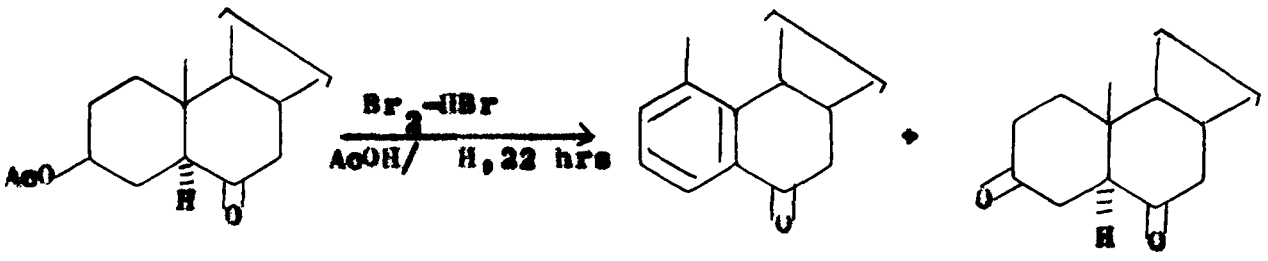
∝-Bromination

Previous work from these laboratories described the ∝-bromination of 3-acetoxy-5∝-cholestan-6-one (CLIV)[133] with bromine, acetic acid-ether at room temperature. This reaction afforded 3β-acetoxy-5,7,7-tribromo-5∝-cholestan-6-one (CLV) and sometimes, also 3β-acetoxy-5,7β-dibromo-5∝-cholestan-6-one (XXXV).



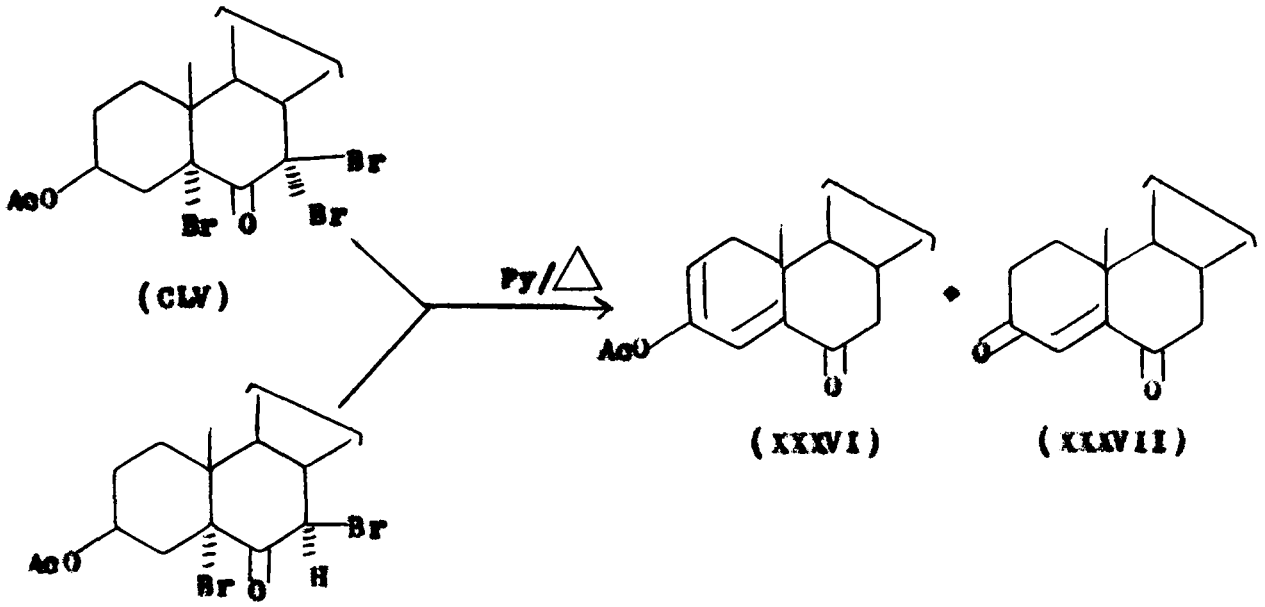
(CLIV) (CLV) (XXXV)

3β-Acetoxy-5∝-cholestan-6-one (CLIV) on heating with Br_2/HBr in ether-acetic acid for 22 hrs provided the product of ring A aromatization, 1-methylcholesta-1,3,5(10)-trien-6-one (CLVI) and 5∝-cholestan-3,6-dione (CLVII).[133]



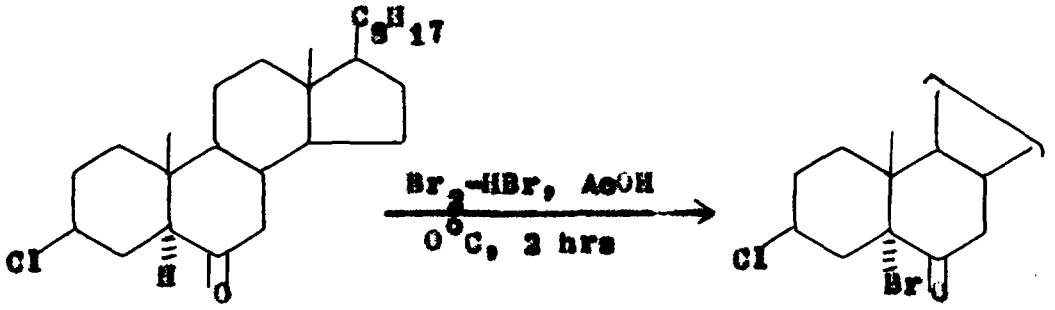
(CLIV) (CLVI) (CLVII)

Interestingly, both the compounds (CLV) and (XXXV) on pyridine dehydrobromination gave 3—acetoxycholesta-2,4-dien-6-one (XXXVI) and cholest-4-ene-3,6-dione (XXXVII), an artefact of (XXXVI).

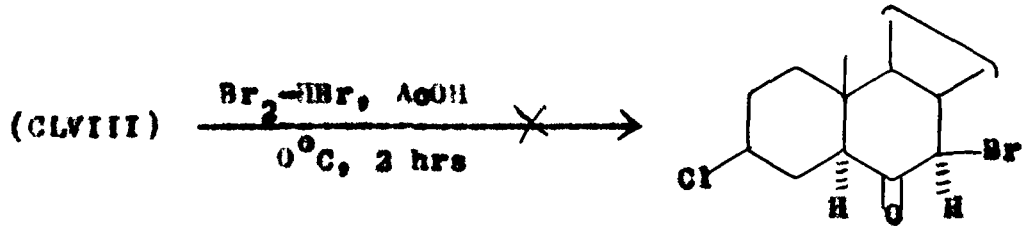


In continuation of above work and in anticipation of some interesting results, 3β-chloro-5α-cholestan-6-one (CLVIII) was subjected to α-bromination under different conditions of reaction. 3β-Chloro-5α-cholestan-6-one (CLVIII) was prepared according to the literature procedure.[154] The i.r. and n.m.r. spectra of the ketone (CLVIII) were determined for total identification and for the purpose of comparison with the bromination products obtained from it. The i.r. spectrum showed bands at ν max. 1720 (C=O) and 755 cm^{-1} (C-Cl) stretching respectively. The n.m.r. spectrum (60 MHz) of the ketone (CLVIII) gave broad multiplet centred at

δ3.8 which was assigned to C_3 proton (α) , axially oriented. The half band width ($W_{\frac{1}{2}}$ = 20 Hz) further supports the axial orientation of C_3 proton (α) and implies trans ring junction (A/B). There was no signal corresponding to C_5 proton (α) suspected to be merged with methylene envelop in the region δ 1.0-2.4. The methyl signals were observed at δ 0.88 (C_{10}-CH_3), 0.83 (C_{13}-CH_3) and 0.75, 0.78. The bromination of the ketone (CLVIII) with Br_2/HBr in ether-acetic acid at about 0°C for 2 hrs, afforded a solid compound, m.p. 124-25° in about 80% yield.

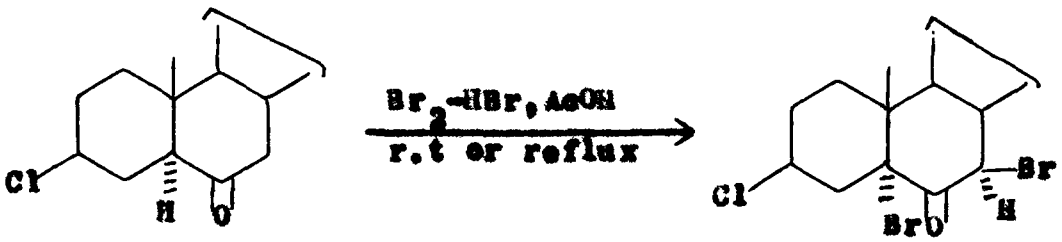


(CLVIII) (CLIX)



(CLX)

The bromination of the ketone (CLVIII) under essentially the same conditions of solvents and reagents but at room temperature and reflux temperature gave a different product of bromination, m.p. 174-75°, in about 85% of yield.



(CLVIII) (CLXI)

Characterisation of the compound, m.p. 124-25° as 3β-chloro-5α-bromocholestan-6-one (CLIX)

The compound, m.p. 124-25°, analysed correctly for $C_{27}H_{44}OClBr$ (positive Beilstein test). From the elemental analysis it was evident that only one bromine atom had been introduced at α-position to the C6-carbonyl group. The i.r. spectrum showed bands at 1712 (C=O) 765 (C-Cl) and 640 cm^{-1} (C-Br)[155]. The equatorial configuration of C3-chlorine bond was substantiated by its i.r. value at 765 cm^{-1} which is compatible with an equatorial chlorine since it is reported that an equatorial chlorine in cyclohexane gives a higher value than the corresponding axial one (590-690 cm^{-1})[155,156].

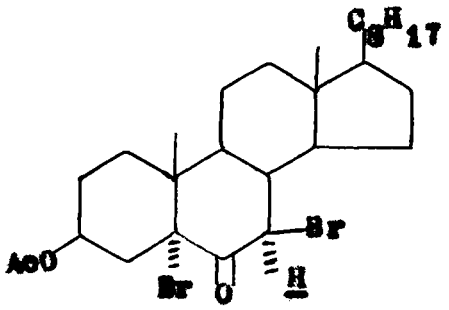
Regarding the assignment of configuration of α-bromine, it was observed in the i.r. spectrum of the compound (CLIX) that the bromine introduced does not affect the normal carbonyl frequency. It is an indication that the bromine assumes the axial orientation rather than equatorial one which is known to cause substantial displacement of the normal carbonyl absorption band towards the higher frequency[155]. Further it was seen that the axially oriented bromine absorbs at lower frequency than its corresponding equatorial

counterpart[156]. However, in order to know whether the axial bromine occupies C5 or C7 positions, its n.m.r. (60 MHz) spectrum was examined. It exhibited a broad signal at δ 4.5 integrating for one proton with a half band width of 21 Hz[157]. This signal is ascribable to C3- axial proton (α) which implies a trans ring junction. In the compound (CLX) with bromine equatorially substituted at C7, the C7 proton would have appeared at a lower field. There was no signal corresponding to this proton which further excludes the possibility of the structure (CLX). The downfield shift of C3-axial proton relative to compounds where there is no bromine at C5, further supports the position and orientation of bromine at C5 which affects C3-proton signal across the space. A multiplet centred at δ 2.47 integrating for two protons has been assigned to C7-methylene group α to C6 keto function. On the basis of the foregoing discussion, it is inferred that the compound, m.p. 124-25° has the structure (CLIX). Methyl signals were observed at δ 1.0s ($C10-CH_3$), 0.69s ($C13-CH_3$), 0.9 and 0.85.

Characterisation of the compound, m.p. 174°, as 3β-chloro-5,7β-dibromo-5α-cholestan-6-one (CLXI)

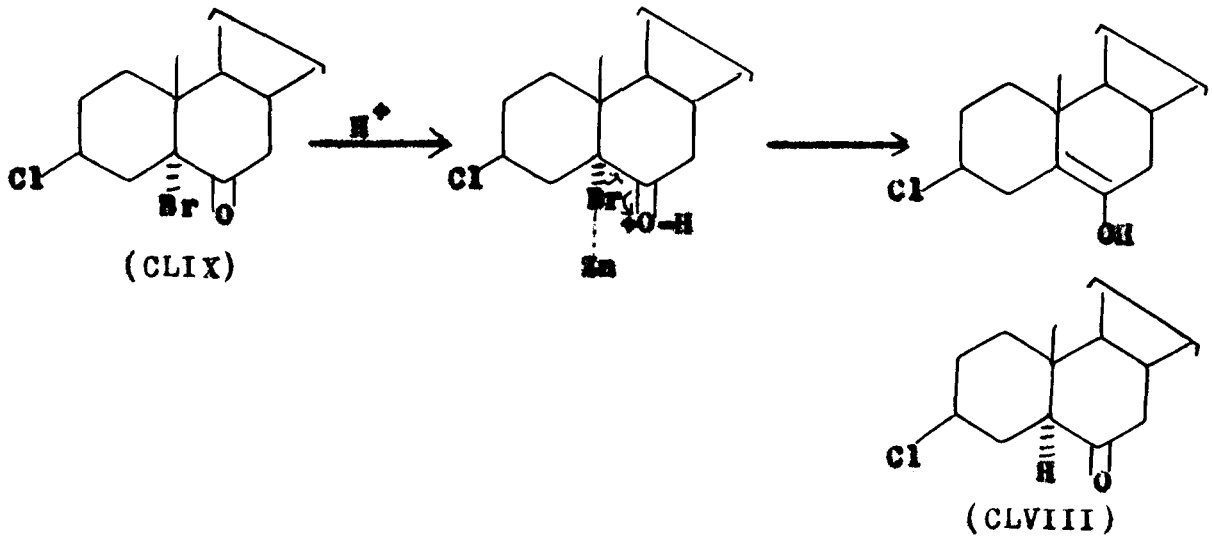
The compound, m.p. 174°, analysed correctly for $C_{27}H_{43}OClBr_2$ and gave a positive Beilstein test for halogens. The elemental analysis revealed that in this compound two bromine atoms were incorporated at α-positions to C6-carbonyl group. The i.r. spectrum of the compound (CLXI) exhibited bands at 1725 (C=O), 736 (C-Br;

equatorial bromine) and 655 cm^{-1} (C-Br; axial bromine)[155]. The equatorial substitution of bromine at C7 was very clearly supported by a shift of carbonyl band to a higher frequency[153,158]. An axial α-bromine does not make any appreciable influence on the position of carbonyl band, as has been observed in the compound (CLIX) discussed earlier. The n.m.r. (60 MHz) spectrum of the compound (CLXI) displayed a doublet at δ 5.35 for one proton. This observation very decisively supported that bromine at C7 is equatorial and the axial C7 proton (α) is split by C8-axial proton (β) to a magnitude of 9 Hz[157]. Another broad signal at δ4.39 is ascribable to C3-axial (α) proton. Here also this signal is shifted downfield because of the presence of axial bromine at C3 as seen in the case of bromoketone (CLIX). The methyl signals were observed at δ 1.1s ($C10-CH_3$), 0.72s ($C13-CH_3$), 0.95 and 0.84. This structural assignment finds further support from the n.m.r. spectrum of similarly constituted bromoketosteroid (XXXV) previously obtained by Ahmad et al.[153] In this case (XXXV) also the C7-axial (α) proton appears at δ 5.36 as a doublet with a J value of 95 Hz due to its coupling with C8-axial (β) proton. The shift of carbonyl band to higher frequency induced by C7-equatorial (β) bromine noted in the compound, m.p. 174° also gets support from a similar shift seen in the i.r. spectrum of the compound (XXXV).



(XXXV)

The chemical support in favour of the α-brominated products (CLIX) and (CLXI) was obtained by zinc-acetic acid α-debromination to regenerate the respective starting ketone (CLVIII). This implies that the bromine (α) at C5 in the compound (CLIX) is replaced by an axial hydrogen. In dibromoketosteroid (CLXI) both the bromine atoms at C5 and C7 are replaced by the axial and equatorial hydrogens respectively. This observation leads to the fair conclusion that α-bromination and debromination involve a common intermediate which is most likely an enol. This is in fairly good agreement with that predicted to result from the protonation of the Δ^5- or Δ^6-enols in (CLIX) and (CLXI) and simply be a case of electrophilic substitution with retention of configuration[8].

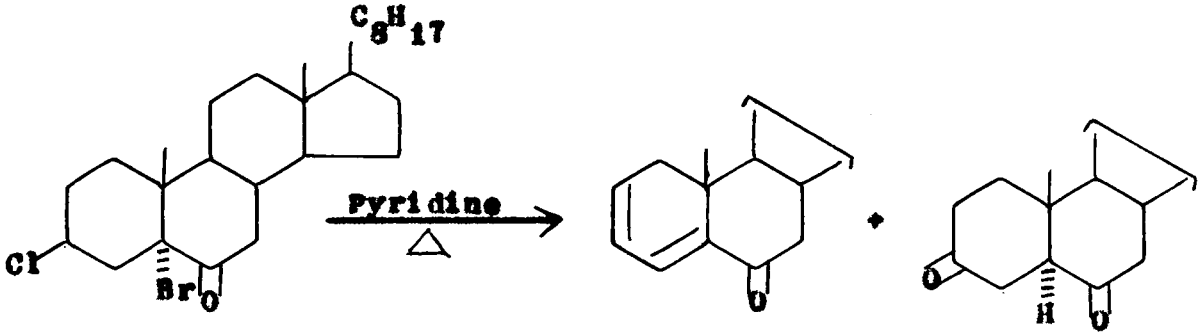


(CLIX) (CLVIII)

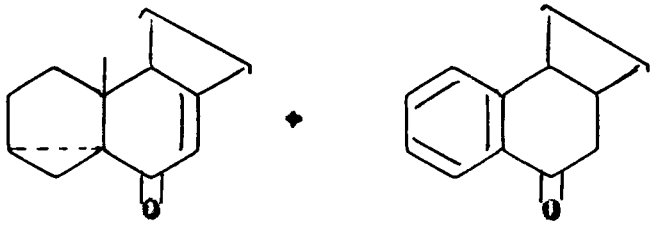
The similar mechanism is applicable in the case of dibromoketone (CLXI).

Dehydrohalogenation of 3β-chloro-6α-bromocholestan-6-one (CLIX)

The haloketone (CLIX), m.p. 124-25°, was subjected to dehydrohalogenation with refluxing pyridine for 12 hours and after usual work up of the reaction mixture, it gave four compounds as revealed by t.l.c. Column chromatography of the crude reaction mixture afforded four well crystalline products, m.p. 128°, 168°, 119° and 110°, respectively.



(CLIX) (CXXXV) (CLVII)



(CLVII) (CLXIII)

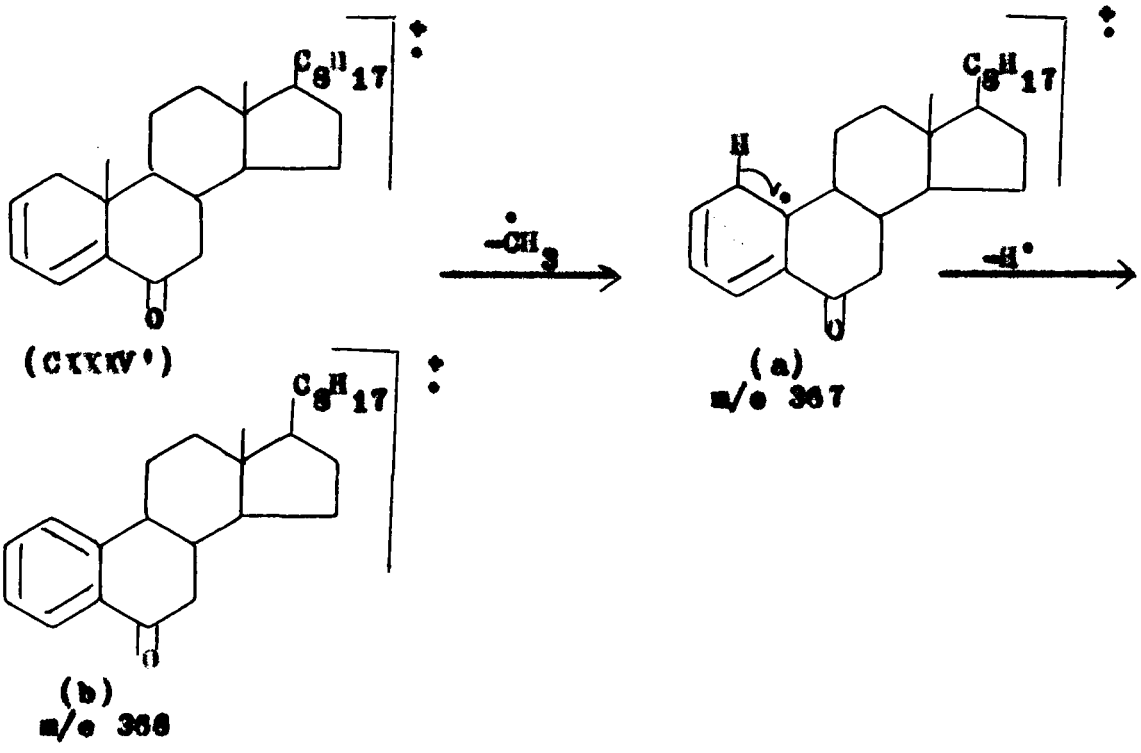
Characterisation of the compound, m.p. 129° as cholesta-2,4-dien-6-one (CXXXV)

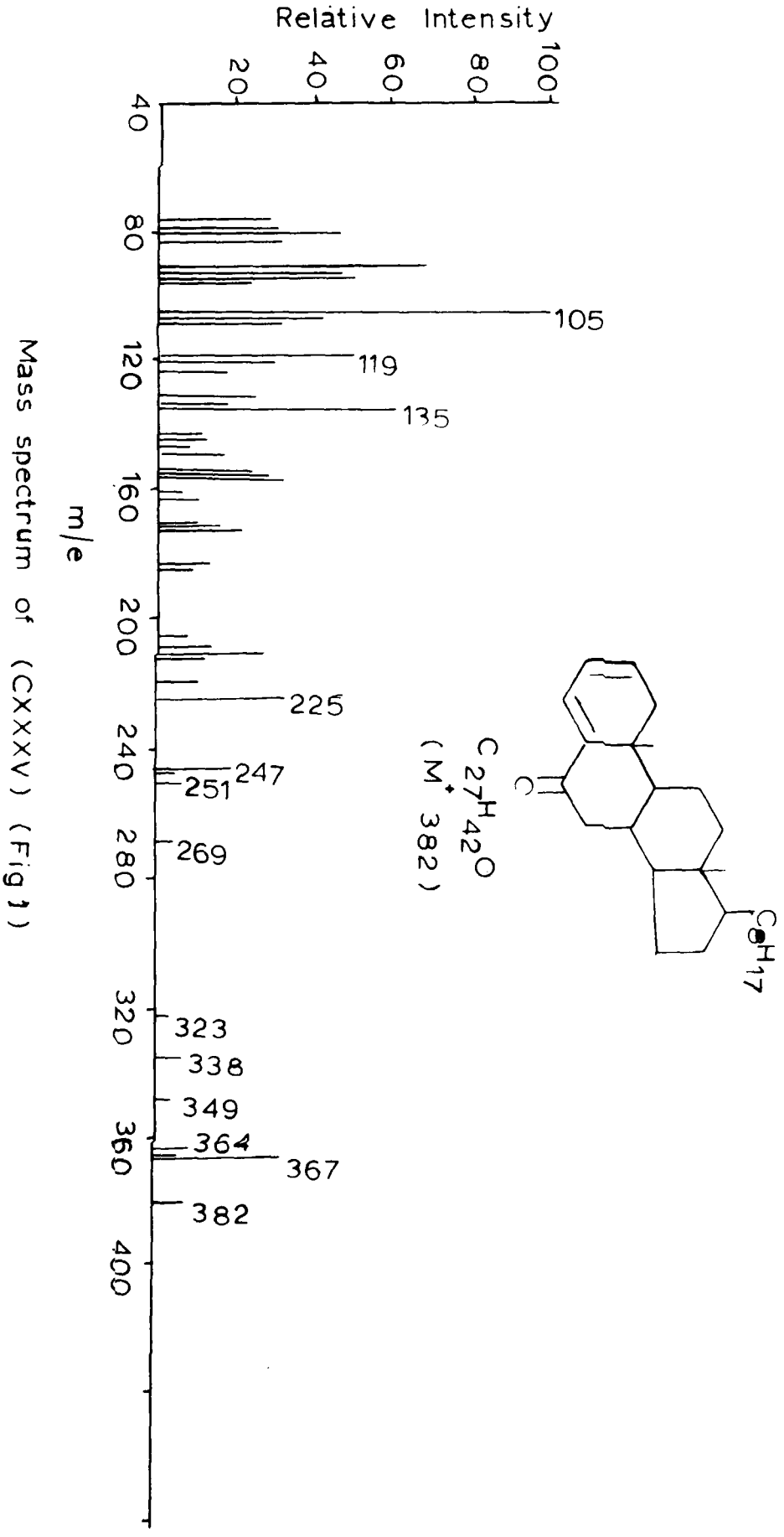
The compound (CXXXV), m.p. 129°, analysed correctly for $C_{27}H_{42}O$ (negative Beilstein test) and its i.r. spectrum showed absorption bands at 1670 (-C=C-C=C-C=O) and 1625 cm^{-1} (C=C).

The presence of conjugated dienone moiety was further supported by its u.v. spectrum (λ max. 314 nm). The n.m.r. spectrum of the compound (CXXXV)[150,159] exhibited signals at δ 6.83 mc (C2-H), 6.13 dist. d (C3-H, C4-H), 2.3 mc (C7-H_2), 1.0 (C10-CH_3), 0.7 (C13-CH_3), 0.95 and 0.83 (other methyl signals). The mass spectrum of the compound (CXXXV)[160] (Fig. 1) gave molecular ion peak at m/e 382 ($C_{27}H_{42}O$) followed by significant peaks at m/e 367 (M-15), m/e 366 (m/e 367-H), m/e 364 (M-H_2O), m/e 349 (m/e 367-H_2O), m/e 338 (m/e 366-CO), m/e 323 (m/e 338-CH_3), m/e 269 (M-C_8H_{17}), m/e 251, m/e 247, m/e 225, m/e 135, m/e 119, m/e 105 (base peak), and lower mass peaks. The formation of some of the salient fragment ions has been shown in the following schemes (Schemes 1-4).

Scheme-1

m/e 367 (M-CH_3) and m/e 336





Mass spectrum of (CXXXV) (Fig 1)

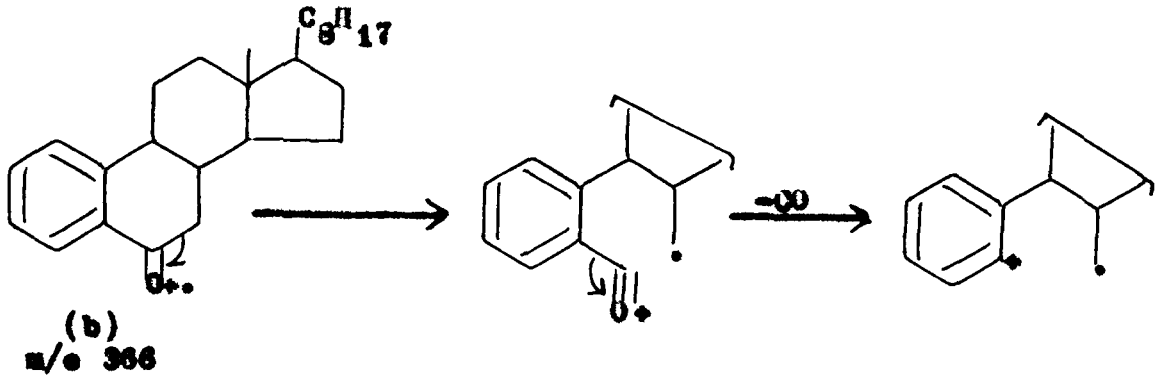
m/e 364 and m/e 349

These two fragment ions represent the loss of water molecule from the molecular ion and the ion m/e 367(a), respectively.

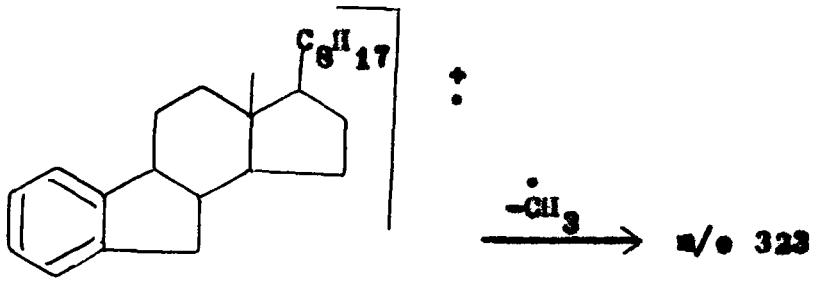
m/e 338 and m/e 323

The ion m/e 338 is compatible with the loss of a molecule of CO from the fragment ion m/e 366. Subsequent loss of a methyl group from the ion m/e 338 will account for the ion m/e 323.

Scheme-2



(b)
m/e 366

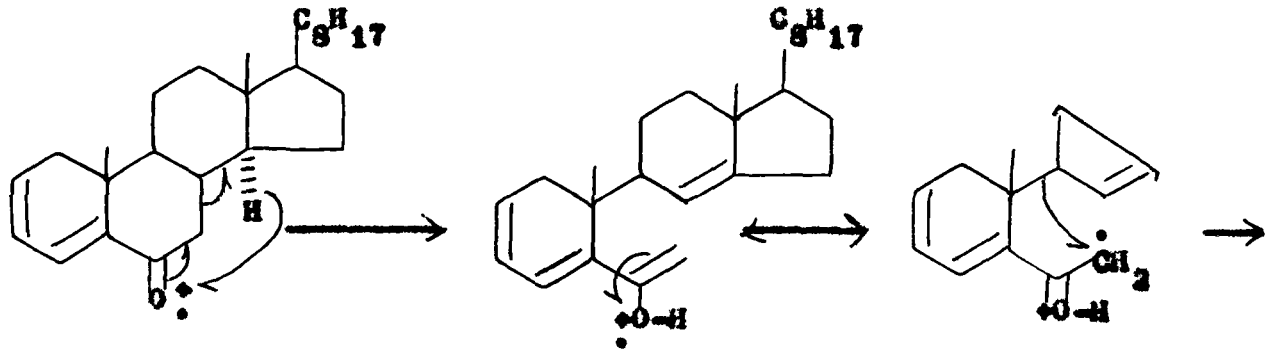


m/e 323

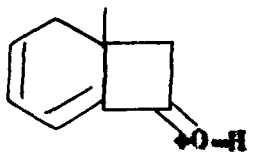
(c)
m/e 338 ($C_{25}H_{38}$)

Scheme-3

m/e 135 and m/e 119

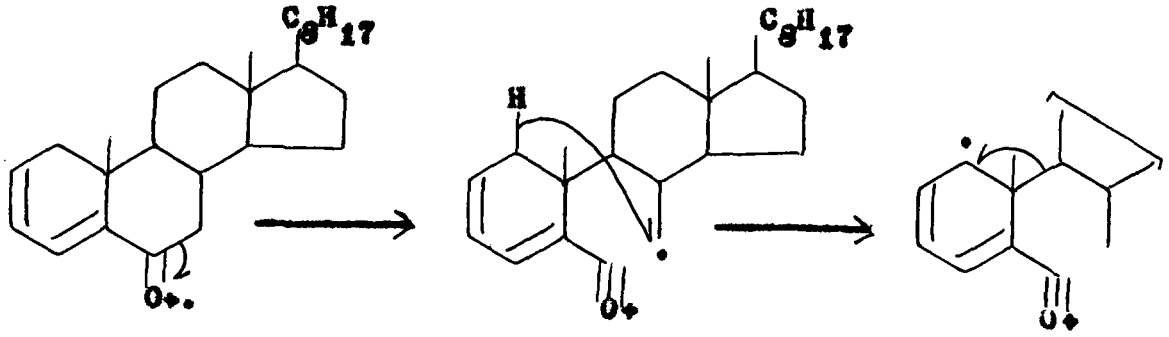


(CXXXV)

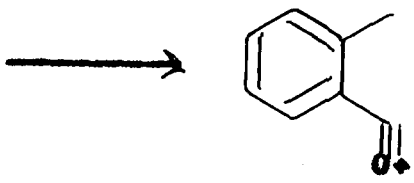


(d)
m/e 135 ($C_9H_{11}O$)

m/e 119



(CXXXVI)

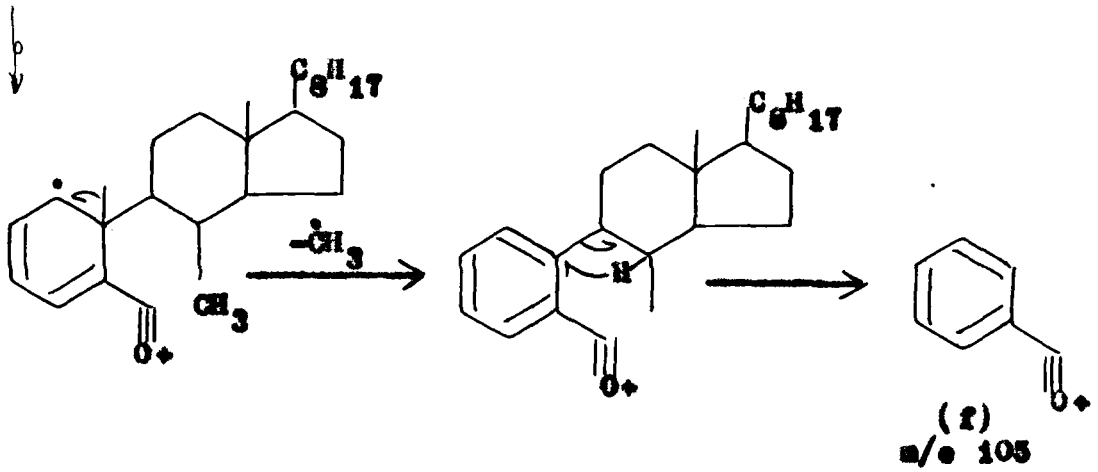


(e)
m/e 119 (C_8H_7O)

m/e 105 (base peak)

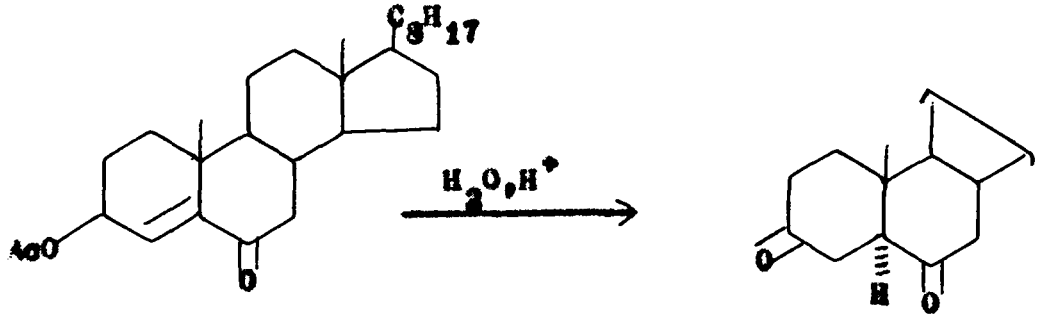
The appearance of a strong peak at m/e 105 is suggestive of the fact that ring A undergoes aromatisation to give benzoyl cation ($C_6H_5\overset{+}{C}O$).

(CXXXV) Scheme - 4



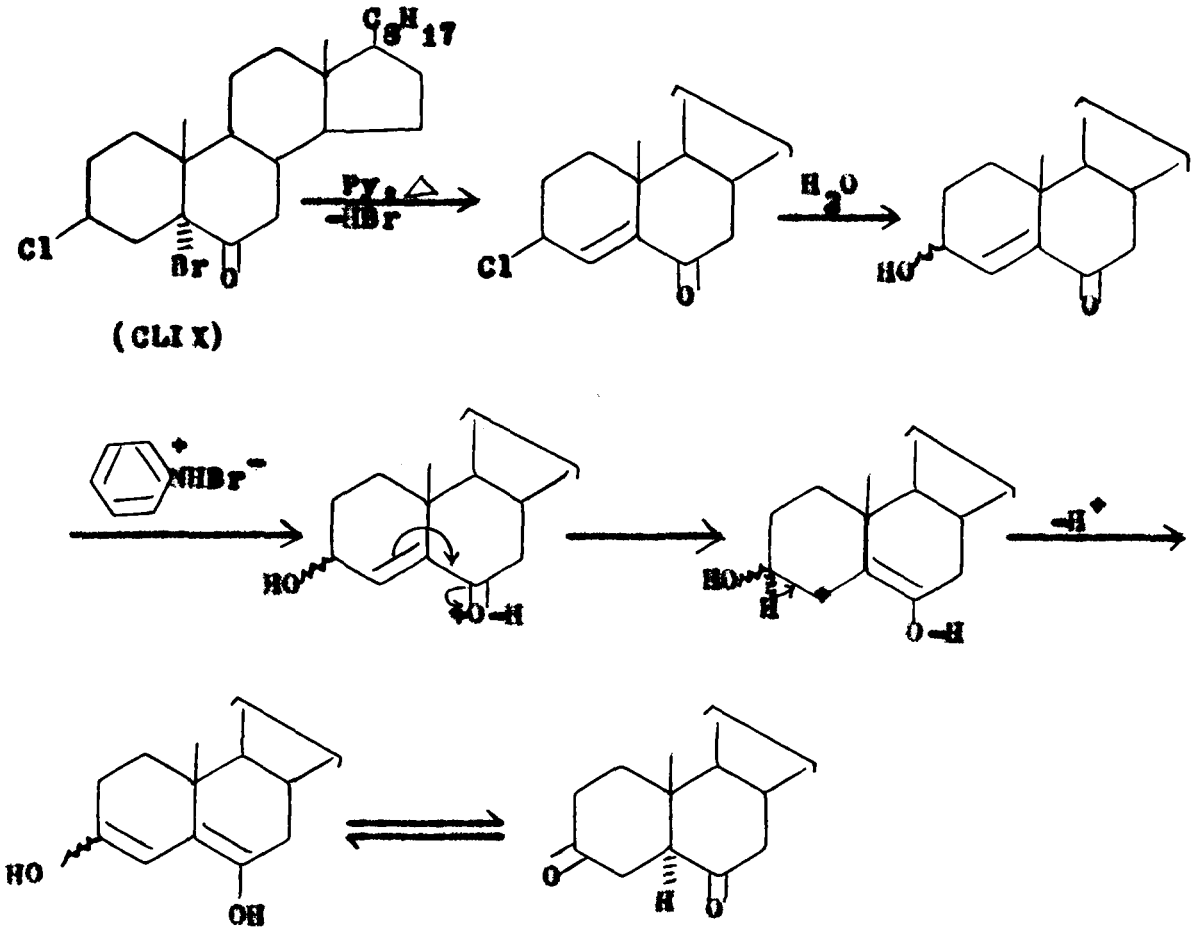
Characterisation of the compound, m.p. 168° as 5α-cholestan-3,6-dione (CLVII)

The compound, m.p. 168° analysed for $C_{27}H_{44}O_2$ (M^+ 400) (negative Beilstein test) and its i.r. spectrum showed a strong peak at 1710 cm^{-1}(-C=O). The n.m.r. spectrum of (CLVII) gave a broad signal spread between δ 2.1-2.7 integrating for 7 protons which can be ascribed to C2-$\underline{H}_2$, C4-$\underline{H}_2$, C5-$\underline{H}$ and C7-$\underline{H}_2$. Other signals were observed at δ 0.9s (3H, C10-$C\underline{H}_3$), 0.70s (3H, C13-$C\underline{H}_3$), 0.93 and 0.90 (other methyl protons). This compound (CLVII) was found to be identical with an authentic sample of (CLVII) prepared according to Heilbron, et al.[161]



(CLXIV) (CLVII)

The formation of (CLVII) from (CLIX) with pyridine under reflux is both interesting as well as intriguing. It appears that traces of water present in pyridine plays an important role in the conversion (CLIX) ⟶ (CLVII). A tentative mechanism for this transformation can be suggested in the following manner.



(CLIX)

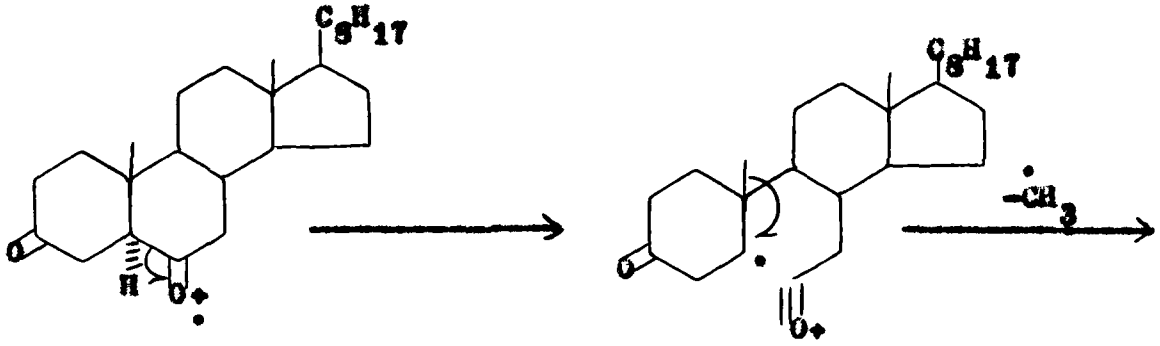
(CLVII)

This mechanism finds support from the observation that the yield of (CLVII) was increased when (CLIX) was heated with pyridin and added aqueous HBr (58%).

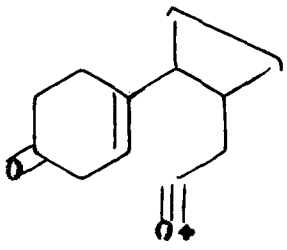
The mass spectrum of 5∝-cholestan-3,6-dione (CLVII) (Fig.2) gave molecular ion peak at m/e 400 ($C_{27}H_{44}O_2$) followed by salient fragment ion peaks at m/e 385 ($M-CH_3$), m/e 382 ($M-H_2O$), m/e 372 ($M-CO$), m/e 331, m/e 329, m/e 287 ($M-C_8H_{17}$), m/e 260, m/e 259, m/e 246, m/e 245, m/e 231, m/e 137 and other lower mass peaks. The genesis of some of the salient fragment ions is shown below (Schemes 5-8).

Scheme - 5

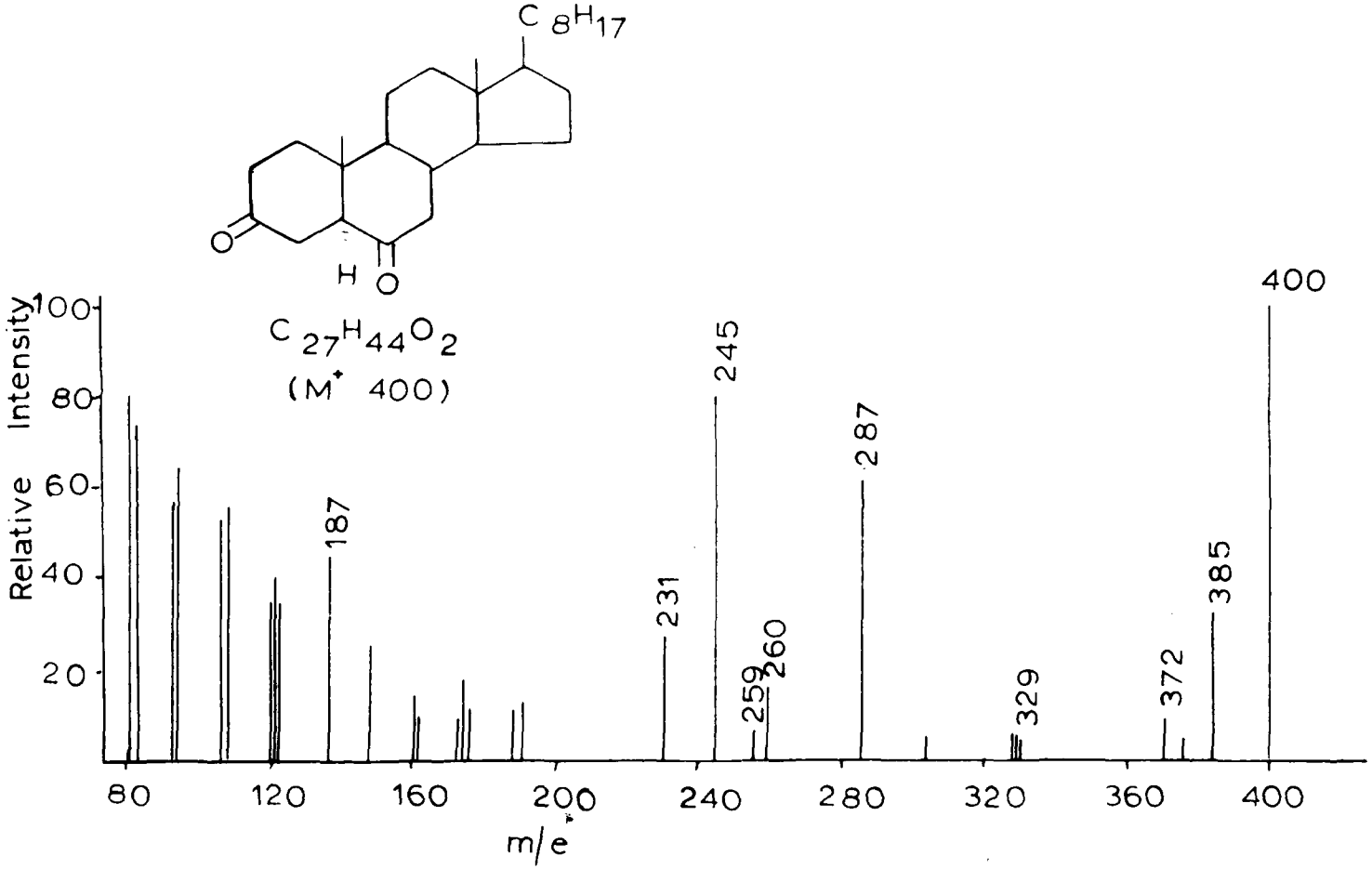
m/e 385 ($M-CH_3$)[162]



(CLVII)



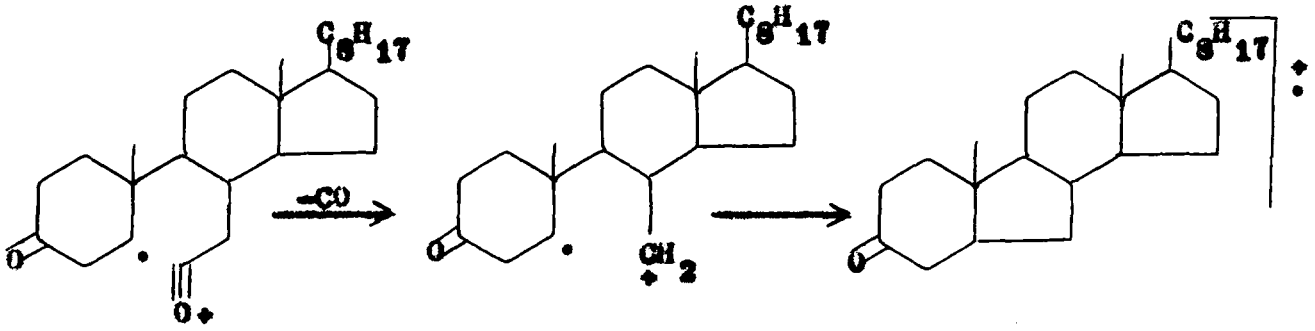
(g)
m/e 385



Mass spectrum of (CLVII) (Fig 2)

m/e 372 (M-CO; $C_{26}H_{44}O$)

Loss of CO may occur either from C3 or C6 ketone or both. As an illustration the expulsion of C6-ketone has been shown below.

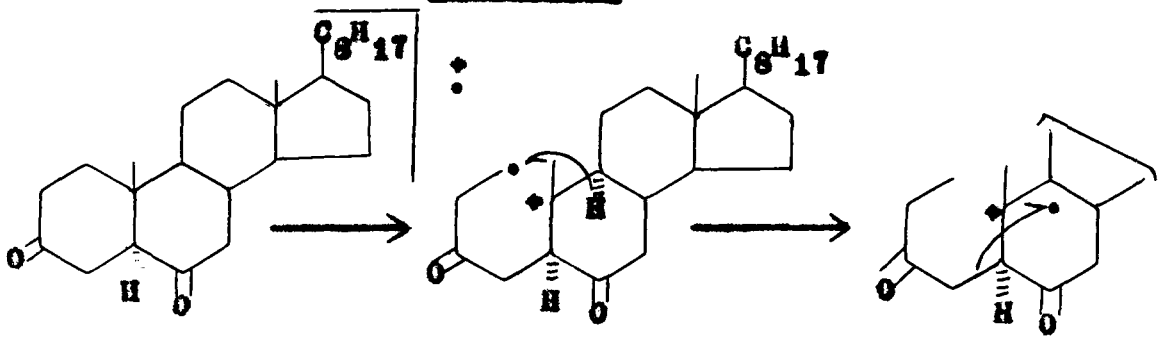


(h)
m/e 372

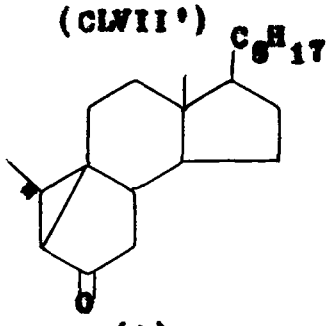
m/e 329

This fragment ion may arise by the loss of ring A, for which several mechanism can be proposed. However, only one mechanism is being given below[161].

Scheme - 6

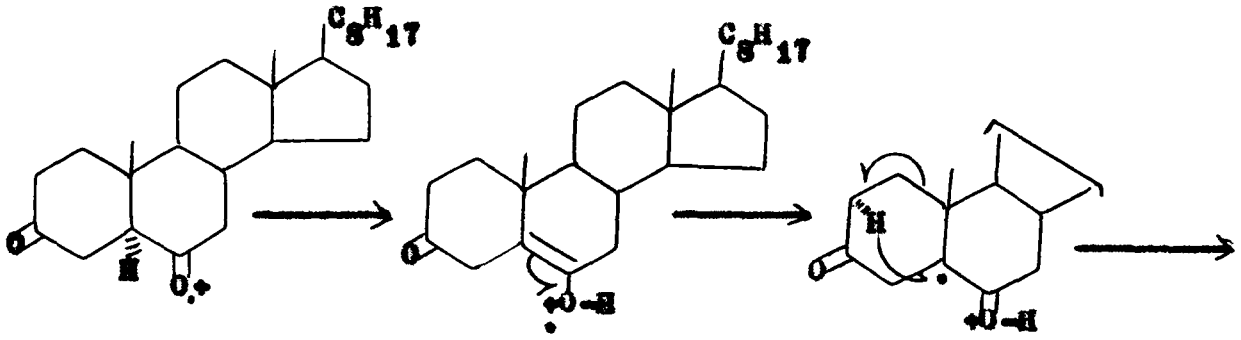


(CLVII')

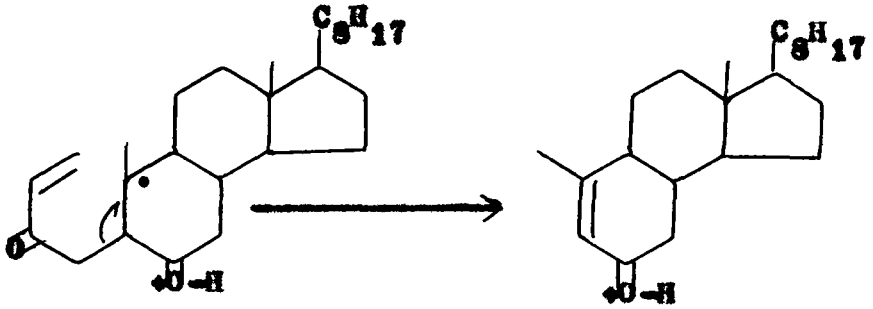


(i)
m/e 329

m/e 331



(CLVII)

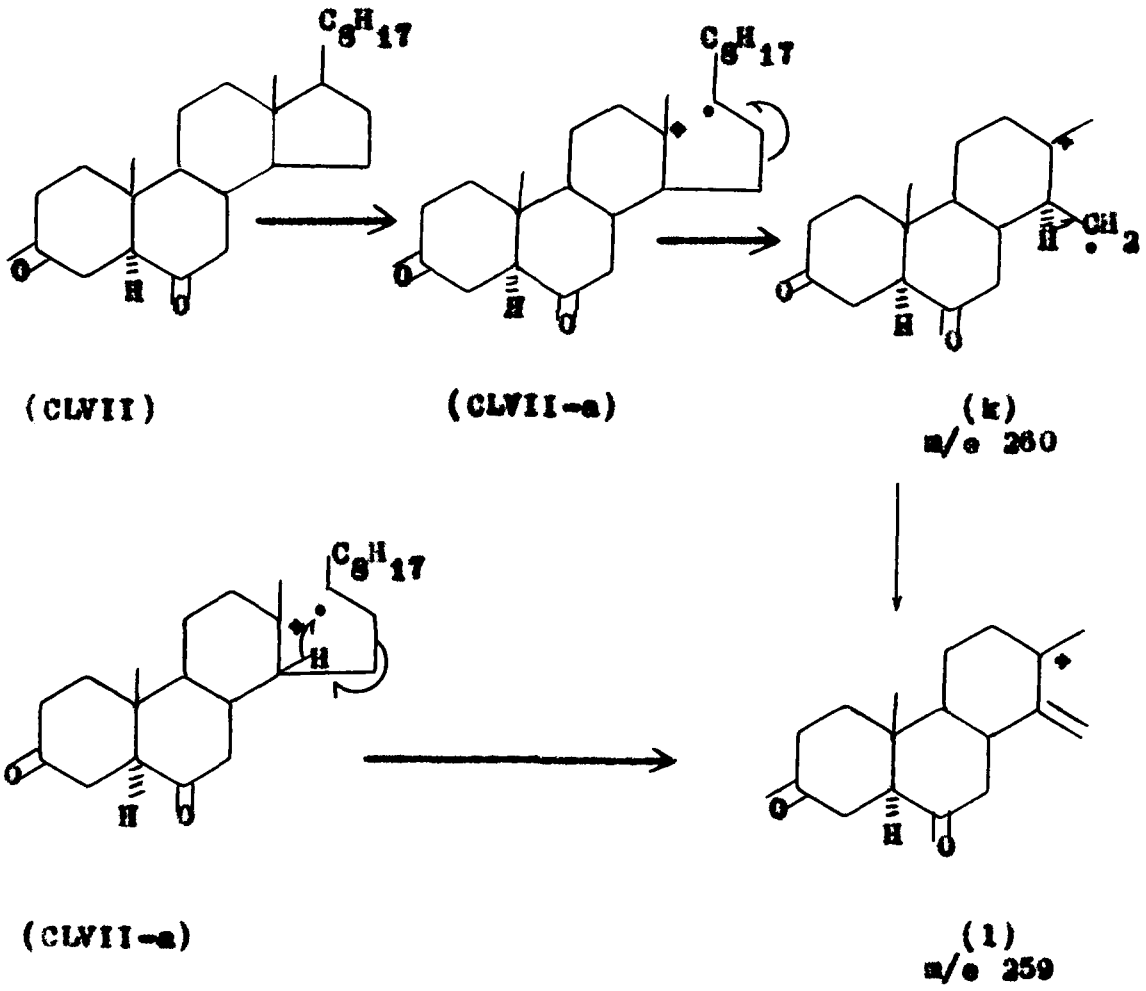


(J)
m/e 331

m/e 259 and m/e 260

These fragment ions result by the loss of the side chain and a part of ring D, as shown below.

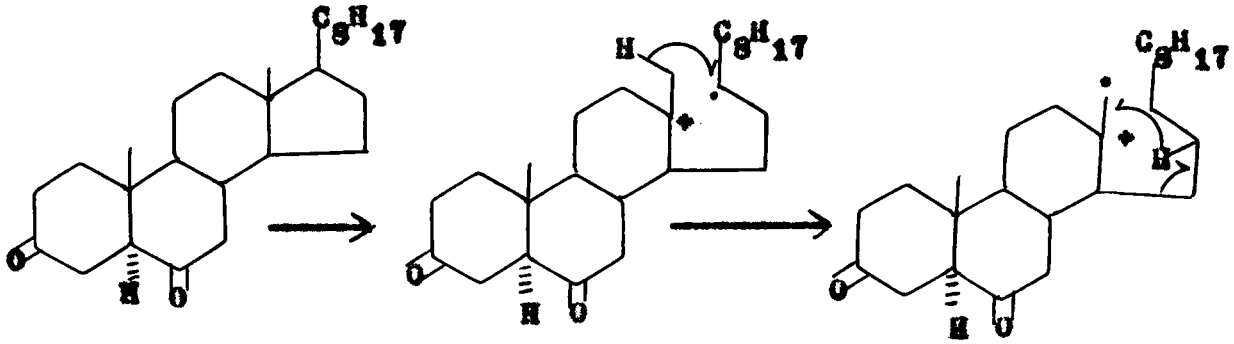
Scheme - 7



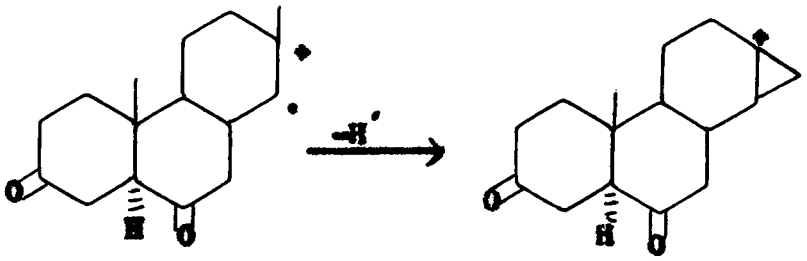
m/e 245 and m/e 246

The fragment ions are formed by the loss of the side chain and ring D.

Scheme - 8



(CLVII) (CLVII-a)



(m) m/e 246 (n) m/e 245

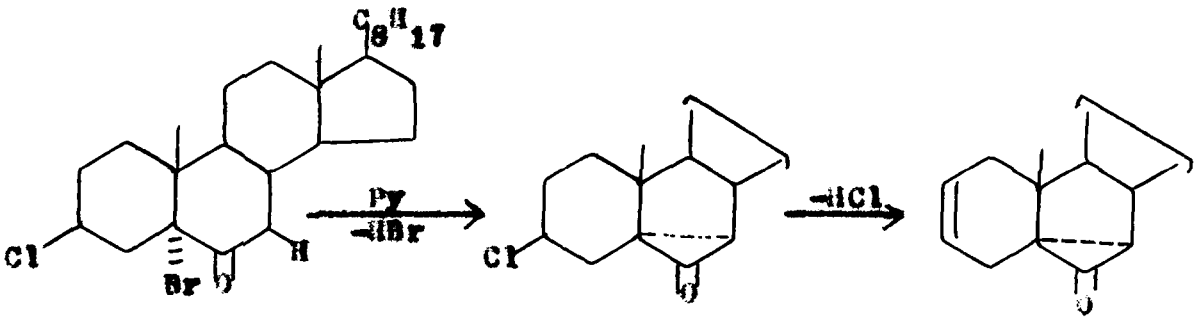
Characterisation of the compound, m.p. 118° as 3α-5-cyclo-5α-cholest-7-en-6-one (CLXII)

The compound (CLXII), m.p. 118° analysed correctly for $C_{27}H_{42}O$ and it gave a negative Beilstein test for halogen. From the elemental analysis, the nature of the substrate (CLIX) and the reaction conditions employed it was suspected that the compound under discussion could be a conjugated diene such as

(CXXXV) obtained by base catalysed elimination of HCl and HBr. The i.r. spectrum of (CLXII) gave a band at 3080w cm^{-1} which can be ascribable to either C=C-H stretching or to a cyclopropane ($\overset{}{C} - \overset{}{C}$ with CH_2) [155,163] moiety in the molecule. Two prominent bands were observed at 1030 and 1010 cm^{-1} which indicated the presence of cyclopropane moiety as in the case of i-cholestane [169]. The presence of a sharp band at 1605 cm^{-1} clearly indicated the presence of a carbon-carbon double bond. The carbonyl peak was observed at 1695 cm^{-1} thus showing that the >C=O group is conjugated with only one carbon-carbon double bond. The conjugated diene (CXXXV) gave i.r. values at 1670 and 1625 cm^{-1} and the spectrum was quite different from the one observed for (CLXII). This therefore necessitated the formulation of the compound, m.p. 118° as distinct from the conjugated dienone (CXXXV). Further the compound, m.p. 119° gave absorption maxima at 252 nm whereas (CXXXV) absorbed at 314 nm. From the i.r. and u.v. values, it is therefore safe to conclude that similar chromophores are not present in (CLXII) and (CXXXV).

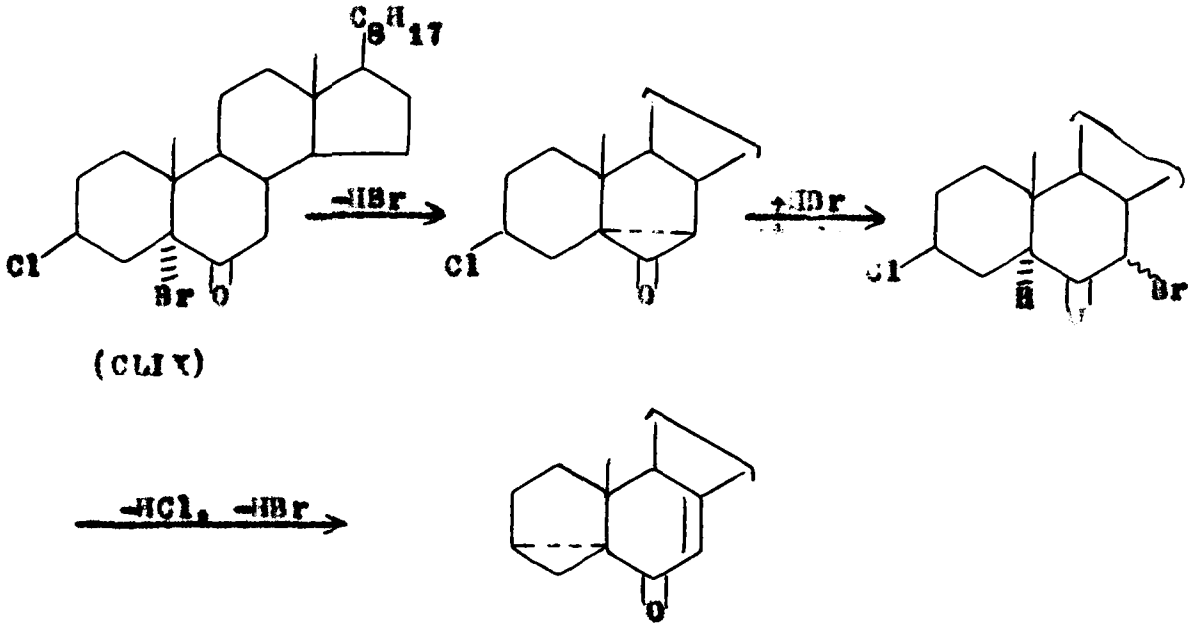
The n.m.r. spectrum of (CLXII)(100 MHz) gave a singlet at δ 6.22 integrating for one proton only. There was no evidence for any other vinylic proton (as would have been demanded by CXXXV). The appearance of a sharp singlet at δ 6.22 indicated that there is no vicinal proton. Another significant signal was observed at δ 2.55 as a multiplet integrating for 2 protons which

can be assigned to two allylic protons such as C9 and C14 protons in (CLXII)[157]. The methyl signals were observed at δ 1.22 (3H, C10-CH_3), 0.76 (3H, C13-CH_3), 1.0, 0.94 and 0.98 (other methyl protons). One of the possibilities from overall reaction conditions and the nature of the substrate (CLIX) would have been the formation of cyclopropane derivative as envisaged in the given scheme.



(CLIX) (CLXV)

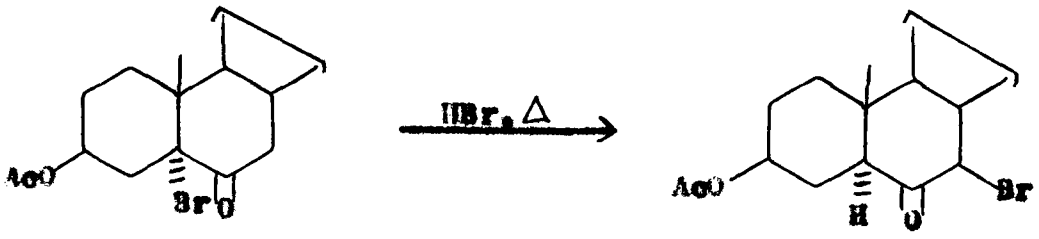
However, such a formulation is untenable in view of the spectral behaviour of the compound, m.p. 118°. Spectral data and elemental analysis demanded that an isomeric structure (with reference to CLXV) be proposed which is compatible with the observed data. The only alternative structure thus, would be (CLXII) which could be shown to have been formed according to the following mechanism.



(CLIV)

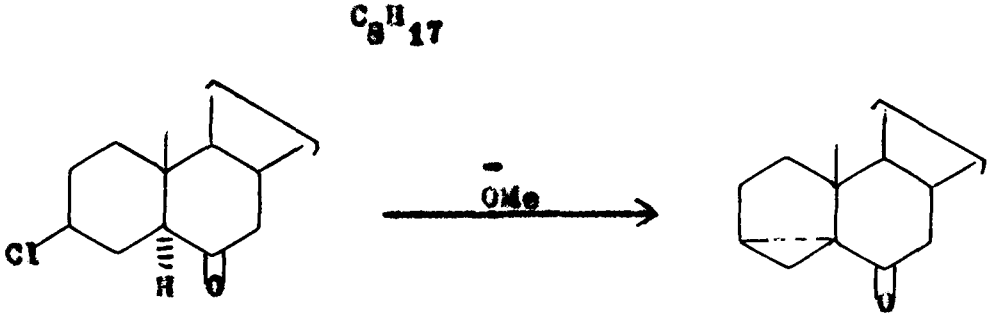
(CLVII)

The structure (CLXII) is compatible with the observed spectral values. It is worth mentioning that isomerisation of 5α-bromo-6-ketones in steroids occurs to give 7-bromo-6-ketones but under acidic conditions[69].



(CLXVI) (CLXVII)

It is also known that 3β-chloro-5α-cholestan-6-one (CLVIII) under basic conditions undergoes 1,3-elimination to give cyclopropane derivative (CVII)[165].



(CLVIII) (CVII)

It is further known that in the n.m.r. spectrum signal for cyclopropane portion need not appear in the region δ 0 - 0.6[157]. It is reasonable to believe that the presence of a keto function at C6-position causes downfield shift of cyclopropane protons thus merging with methylene envelop.

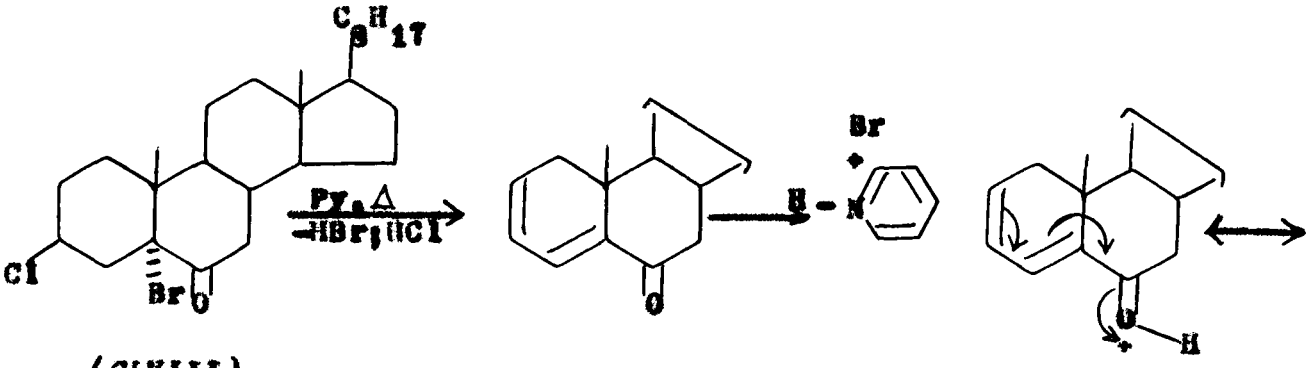
From these arguments it is reasonable to assign structure (CLXII) to the compound m.p. 118°.

<u>Characterisation of the compound, m.p. 110° as 19-norcholesta-1,3,5(10)-trien-6-one (CLXIII)</u>

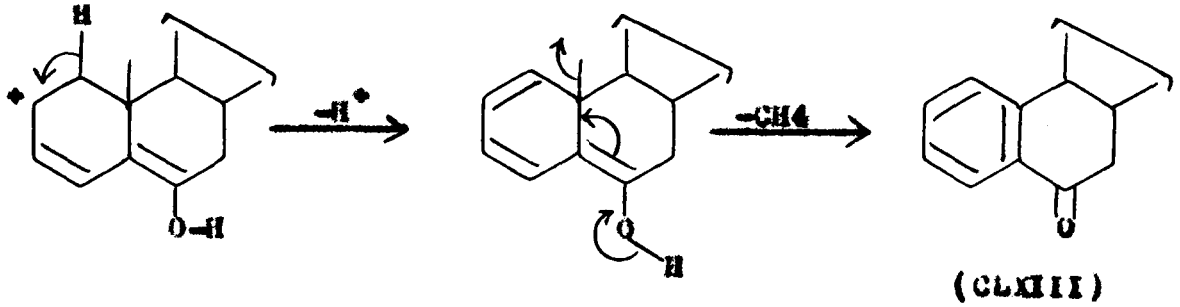
The compound, m.p. 110° (negative Beilstein test) analysed correctly for $C_{26}H_{38}O$. This composition was further substantiated by its mass spectrum which gave molecular ion peak at m/e 366 ($C_{26}H_{38}O$). The i.r. spectrum of (CLXIII) gave bands at 3060 (C=C), 1680 (C=C-C=O) and 1600 cm^{-1} (aromatic system)[153]. The presence

of a carbonyl group attached to a benzenoid ring system was further revealed by the u.v. spectrum which gave absorption maxima at 253 nm together with another band at 295 nm. The presence of an aromatic ring system was further revealed by the n.m.r. spectrum of (CLXIII). It gave signals at δ 8.05m (1H, J = 9 Hz, o-coupled; J=2 Hz, m-coupled), 7.3m (3H, C1-H, C2-H and C3-H), 2.35m (3H, C7-H_2, and C9-H, allylic to 5(10)-double bond)[157], 0.70s (3H, C13-CH_3), 0.83, and 0.92 (other methyl protons). The appearance of the multiplet in the downfield region (δ 8.05) integrating for one proton clearly showed that this one is β - to the C6-keto function.

The formation of (CLXIII) from (CLVIII) can be shown to occur according to the following mechanism.

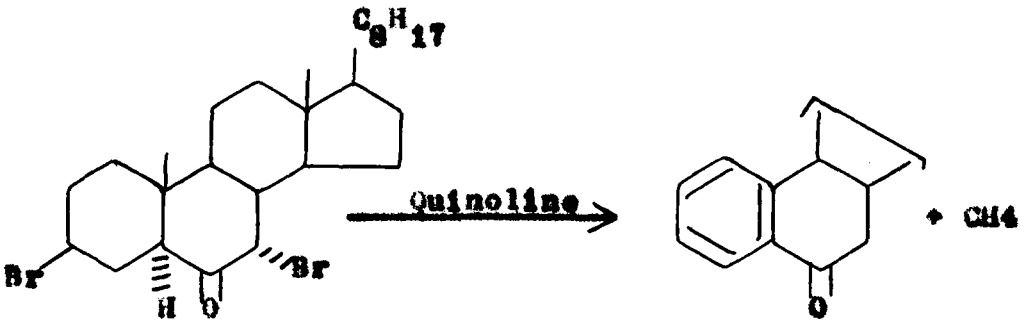


(CLVIII)



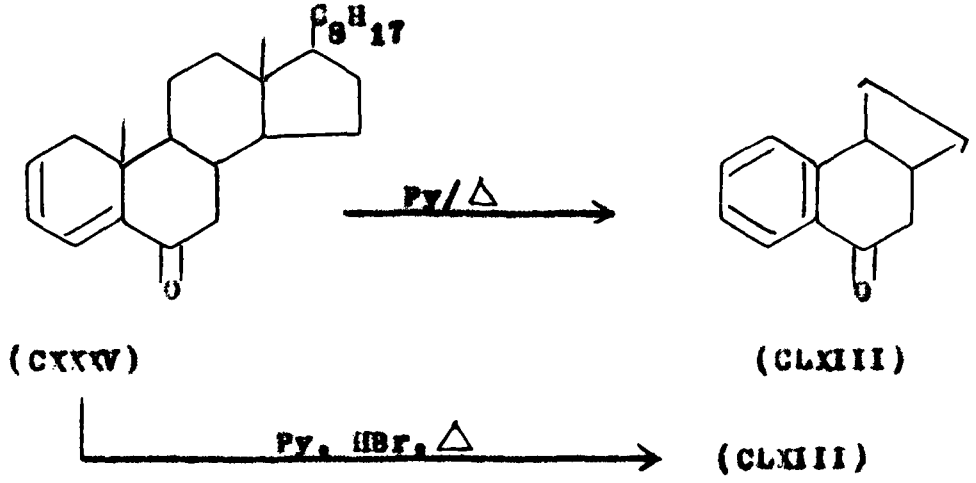
(CLXIII)

The loss of methane molecule in the ring A aromatization has been earlier reported by Hora[166] in the following case. The evolution of methane was detected by mass spectrometry.



(CLXVIII)

The intermediacy of (CXXXV) in the aromatization of ring A was experimentally substantiated. It was observed that when (CXXXV) was heated with pyridine alone under reflux, it did not undergo any change. However when the same reaction was carried out with pyridine containing HBr, (CXXXV) was converted into (CLXIII), thereby supporting the mechanism of aromatization.



(CXXXV) (CLXIII)

(CLXIII)

(Fig.3)

The mass spectrum of (CLXIII) gave the molecular ion peak at m/e 366 ($C_{26}H_{38}O$) followed by other significant peaks at m/e 351, 253, 227, 226, 225, 213, 212, 211, 198, 197, 184, 183, 171, 170, 169, 159, 155, 157, 156, 145, 144, 141, 131, 129, 115, 103 and lower mass peaks. The formation of some of the fragment ions has been rationalised according to schemes given below.

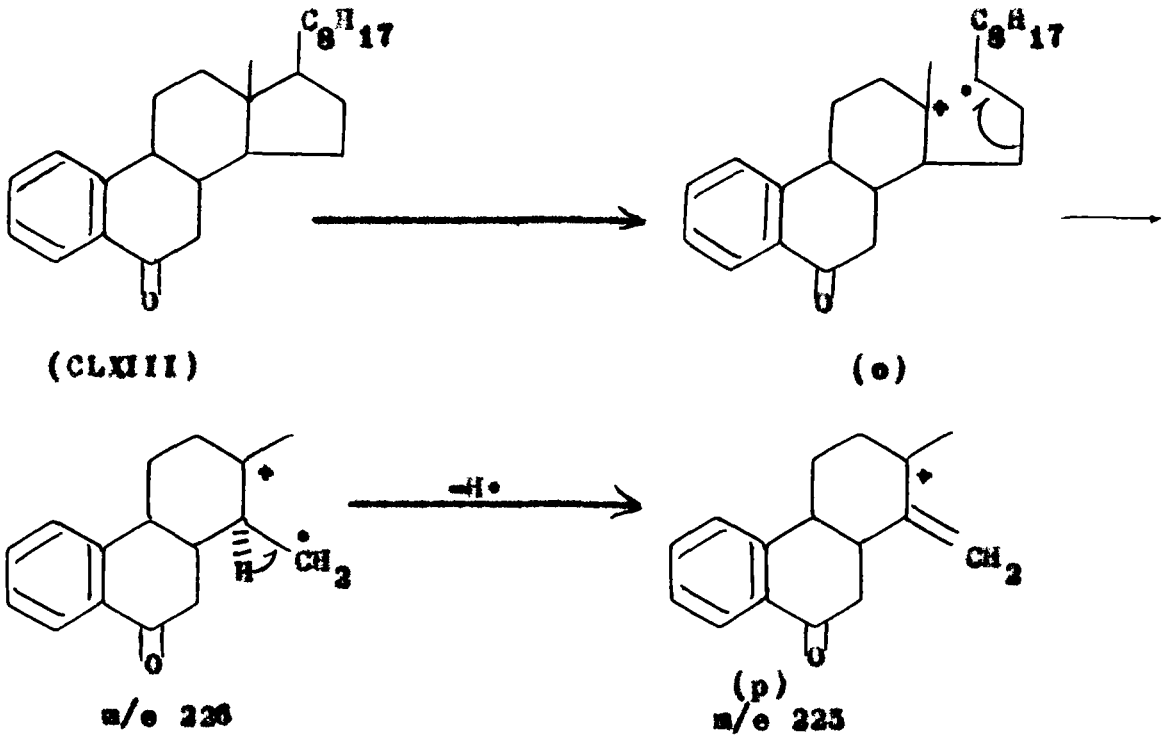
m/e 351 and m/e 255

These fragment ions represent the loss of a methyl group and the side chain (C_8H_{17}; 113), respectively from the molecular ion.

m/e 226 and m/e 225

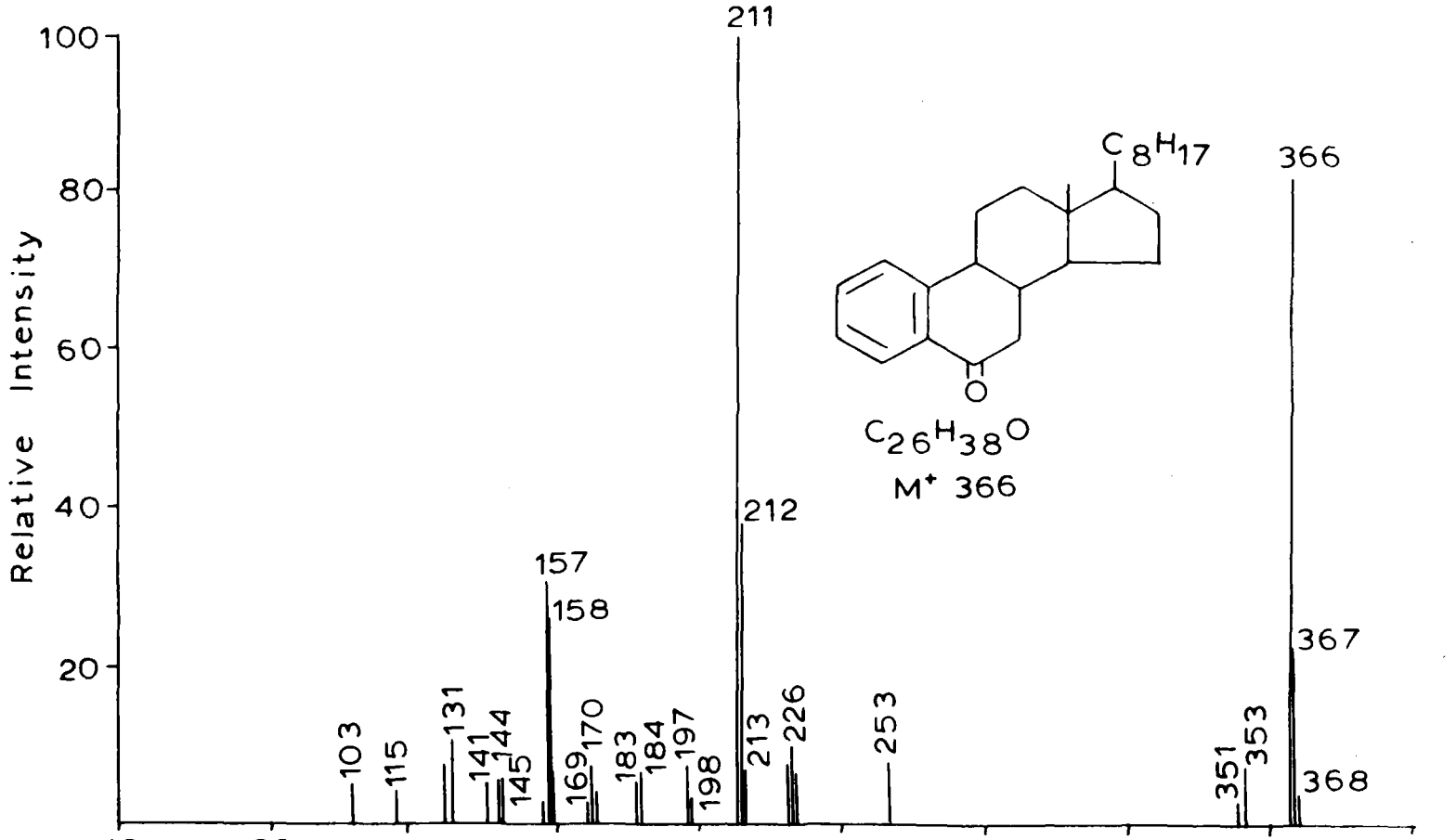
These two fragment ions can be shown to arise according to scheme 9, which result by hydrocarbon-directed fragmentation of the molecular ion.

Scheme - 9



(CLXIII) (o)

m/e 226 (p) m/e 225

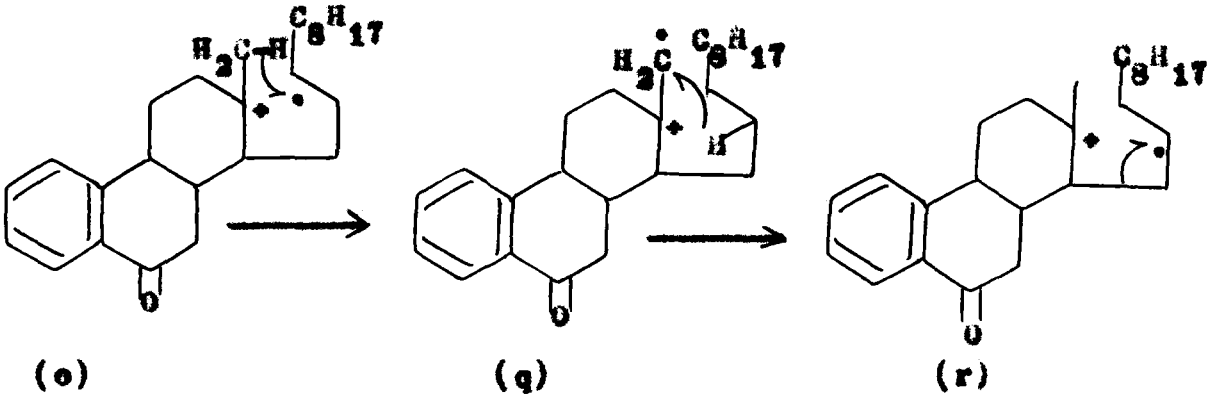


Mass Spectrum of (CLXIII) (Fig.-3)

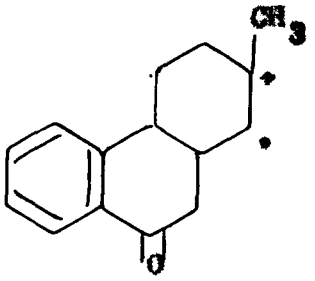
m/e 212 and 211 (base peak)

These fragment ions can once again be shown to be the result of hydrocarbon-directed fragmentation of the molecular ion (Scheme 10).

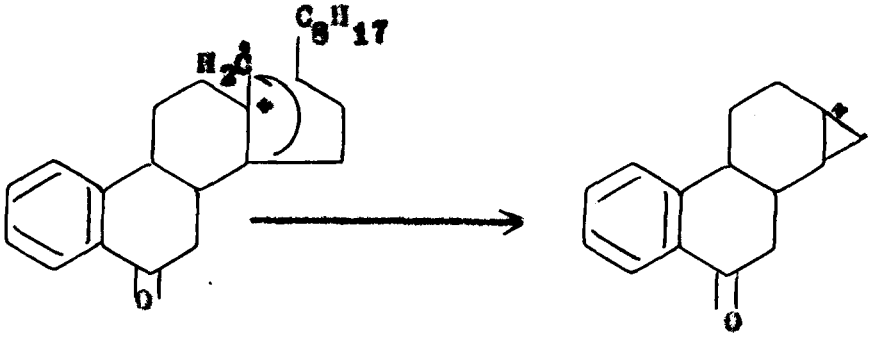
Scheme - 10



(o) (q) (r)



(s)
m/e 212

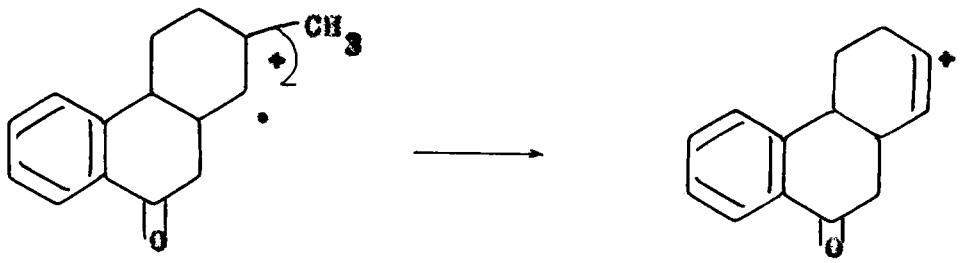


(q) (t)
m/e 211 (base peak)

m/e 197

This fragment ion may be shown to arise by the loss of a methyl group from the ion m/e 212 (Scheme 11).

Scheme - 11



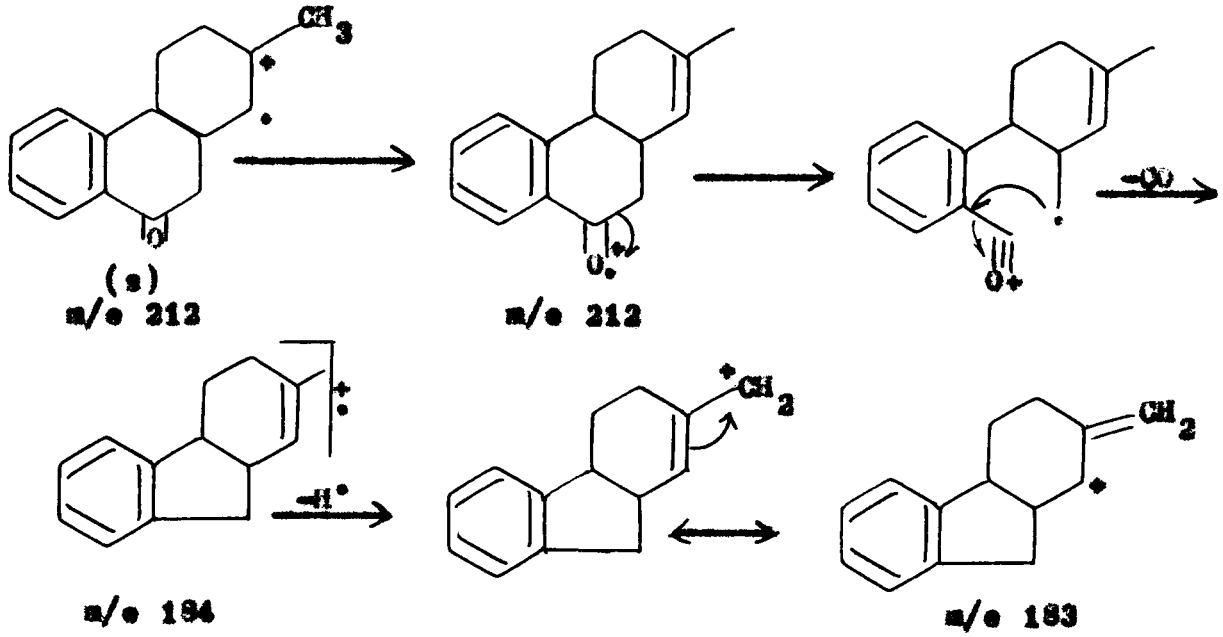
(s)
m/e 212

(u)
m/e 197

m/e 194 and m/e 193

These fragment ions may be the result of the loss of a molecule of carbon monoxide from the ion m/e 212 followed by the loss of one hydrogen atom (Scheme 12).

Scheme - 12



(s)
m/e 212

m/e 212

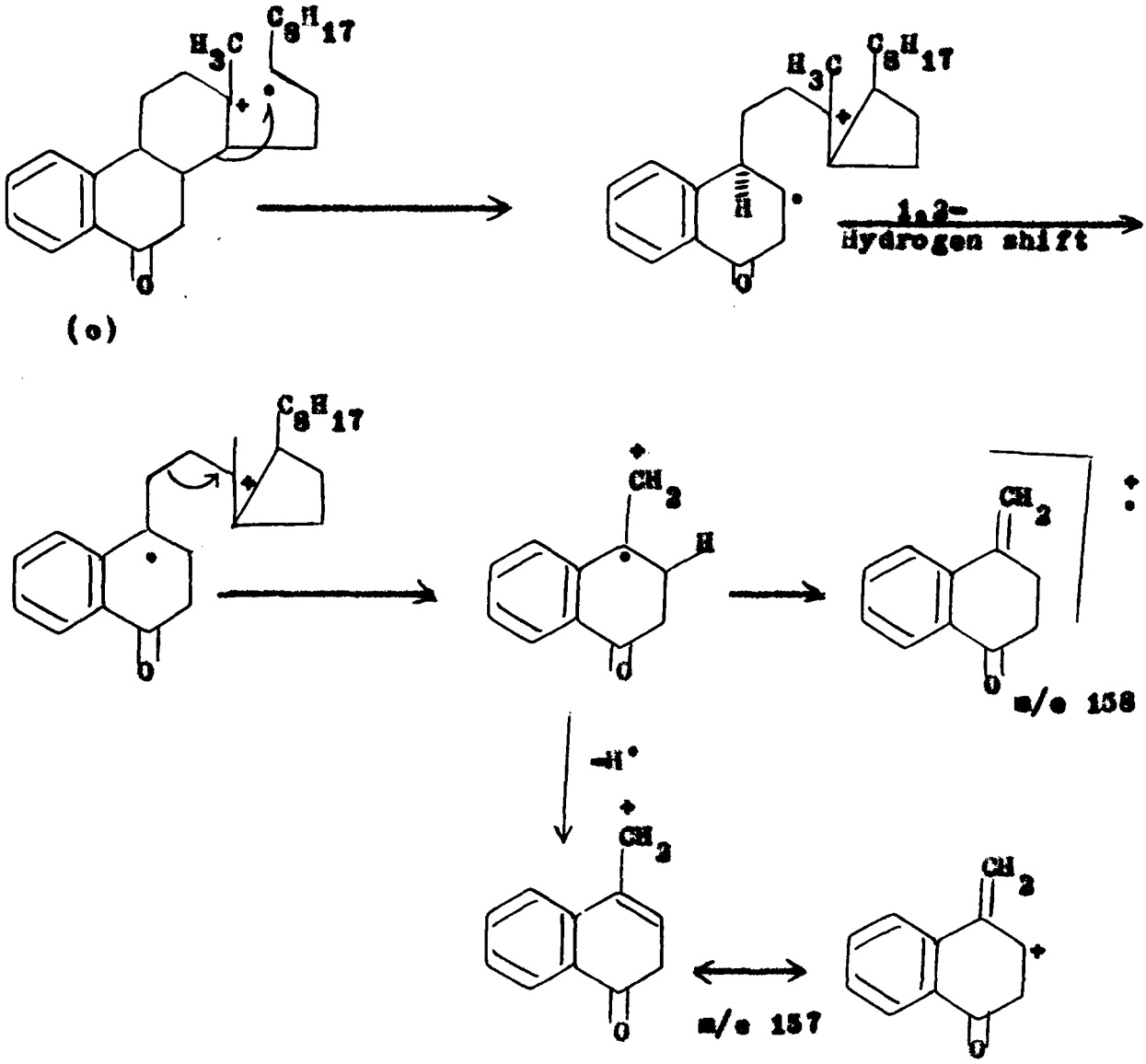
m/e 194

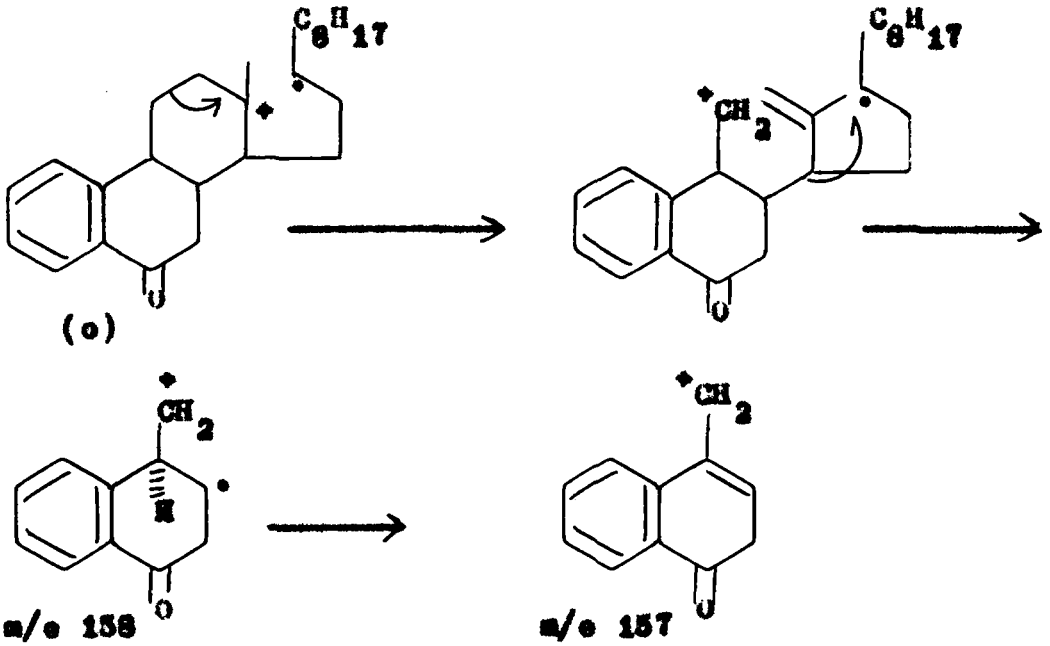
m/e 193

m/e 158 and m/e 157

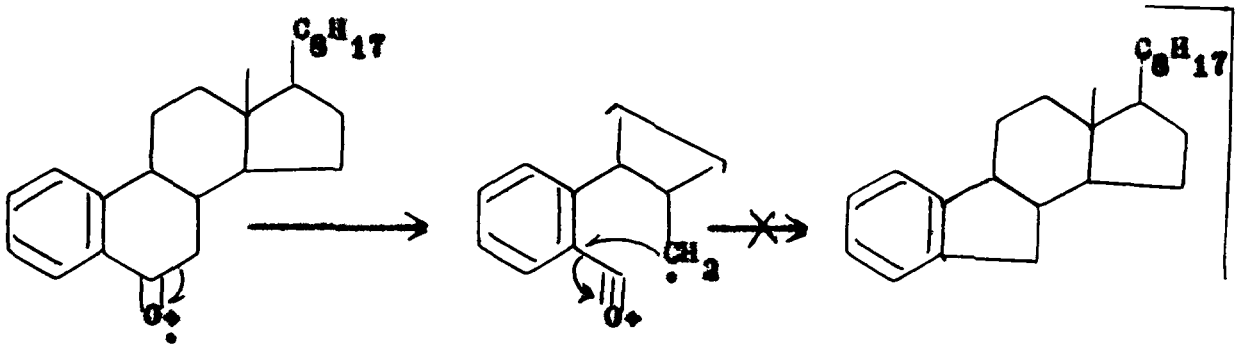
These important fragment ions may be shown to arise from the molecular ion (o) undergoing dissociation in the manner depicted in Scheme 13.

Scheme - 13





It is pertinent to mention that the loss of either carbon monoxide or water from the molecular ion of (CLXIII) was not in evidence. These losses are of common occurrence in cyclic or open chain ketones[167]. One of the possible reason for the absence of M-CO ion would be that it would involve the cleavage of vinylic bond at one stage or the other. This cleavage is perhaps not favourable, at least in the initial stage hence the loss of CO from the molecular ion is not in evidence.



(CLXIII)

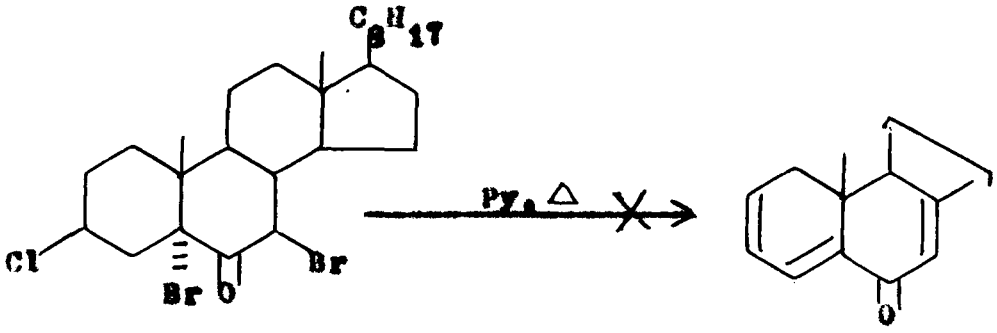
m/e 338

This therefore leads to the formation of all the important fragmentions by hydrocarbon-directed cleavages at the cost of carbonyl-directed fragmentations.

Dehydrohalogenation of 3β-chloro-5,7β-dibromo-5α-cholestan-6-one (CLXI)

The compound (CLXI) was heated under reflux with pyridine to obtain the corresponding dehydrohalogenated product, cholesta-2,4,7-trien-6-one (CLXIX).

In an attempt to obtain cholesta-2,4,7-trien-6-one (CLXIX), the halogenated compound (CLXI) was heated with pyridine under reflux.

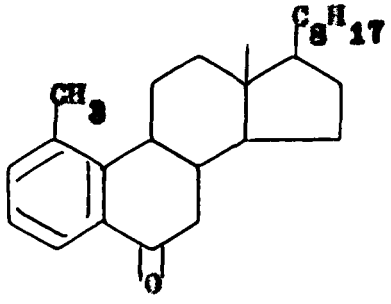


(CLXI) (CLXIX)

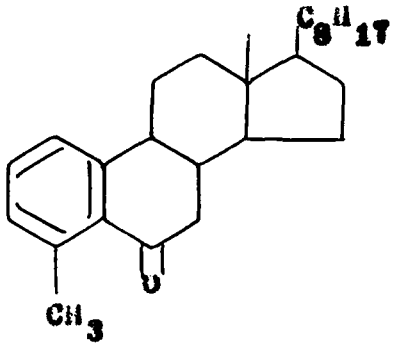
Usual work up of the reaction mixture, followed by column chromatography afforded a single isolable compound, m.p. 140°.

Characterisation of the compound, m.p. 140° as 1-methyl-19-norcholesta-1,3,5(10)-trien-6-one (CLVI)

The compound, m.p. 140° (negative Beilstein test) analysed correctly for $C_{27}H_{40}O$ and its i.r. spectrum gave bands at 3010w (C=C-H), 1685 (C=C-C=O), and 1600 cm^{-1} (C=C, aromatic)[155]. The presence of a carbonyl chromophore conjugated with carbon-carbon double bond was further revealed by its u.v. spectrum (255 nm and 300 nm). The n.m.r. spectrum of the compound, m.p. 140°, gave signals at δ 7.95d,d (1 proton; J=8 Hz, o-coupled and J=2 Hz, m-coupled; C4-H), 7.35m (2H, C2-H and C3-H), 2.41s (3H, C1-CH_3), 0.73 (3H, C13-CH_3), 0.91, and 0.92 (other methyl protons). The appearance of signals in the downfield region (between δ 7.35-7.95 integrating for 3 protons) strongly supported the presence of aromatised ring A. Two possible structures (CLVI) and (CLXX) can be suggested for the compound, m.p. 140°.

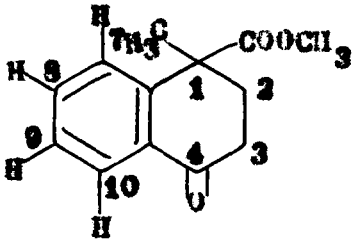


(CLVI)



(CLXX)

A distinction between these two structures (CLVI) and (CLXX) was made with the help of n.m.r. data. The appearance of a signal at δ7.95 (1H) clearly indicated this signal is due to a proton β - to the C6-keto group as in the case of (CLVI). In the alternate structure the β -proton to the carbonyl group being occupied by a methyl group was expected to give a multiplet for 3 protons in the region around δ 7.0. On this basis the compound m.p. 140° has been assigned the structure (CLVI). A comparison of the n.m.r. values of the compound (CLVI) was made with that of 1-methyl-1-carboxymethyl-4-tetralone (CLXXI), where the β -proton to the carbonyl group appeared at downfield relative to other aromatic protons.

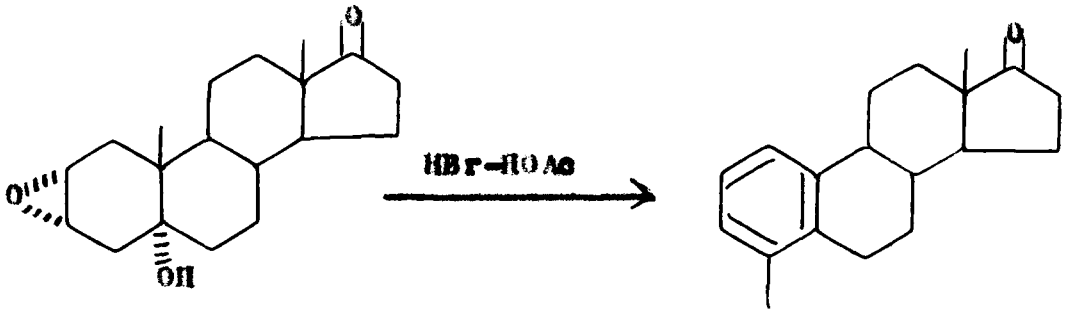


(CLXXI)

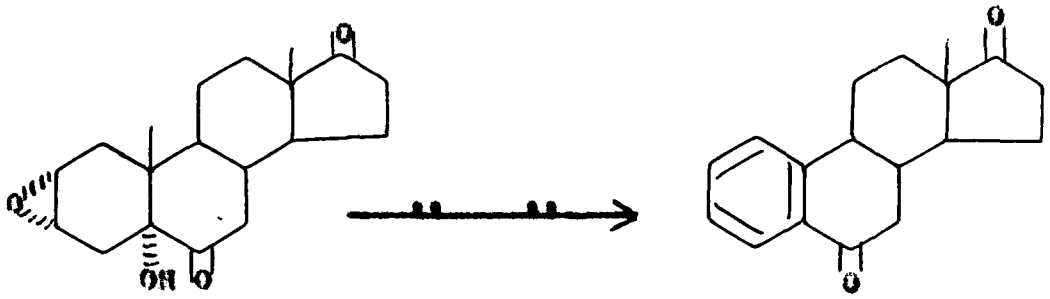
H(7), H(8), H(9)- δ7.41

H(10) δ8.02

It has been recently observed by Hanson[95] that 2α, 3α-epoxy-5α-hydroxyandrostan-17-one (CLXXII) undergoes rearrangement to form 4-methylestra-1,3,5(10)-trien-17-one (LVII) while the corresponding 6-ketone (CLXXIII) affords 1-methylestra-1,3,5(10)-trien-6,17-dione (CLXXIV).



(CLXXII) (LVII)



(CLXXIII) (CLXXIV)

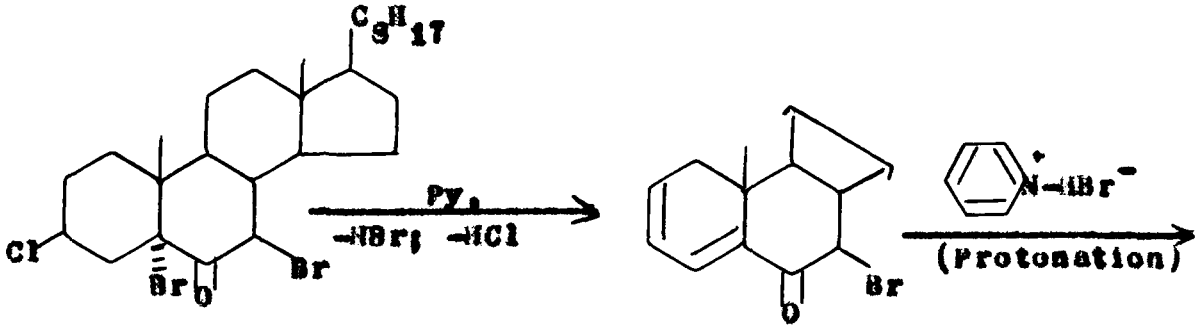
The presence of a 6-carbonyl function in dienone-phenol rearrangements, thus seems to destabilise a C5-carbonium ion and prevents the formation of spirocyclic intermediates. This leads to aromatisation via the alternative pathway of C10→C1 methyl migration.

Further the prerequisite for aromatisation of ring A is the presence of three potential sites of unsaturation in rings A and B.

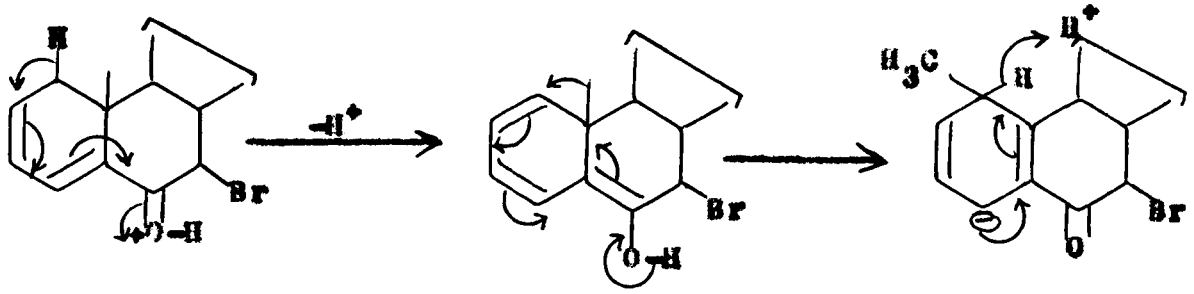
In view of these observations any postulated mechanism should avoid the formation of a C5-cation and subsequent spiro-

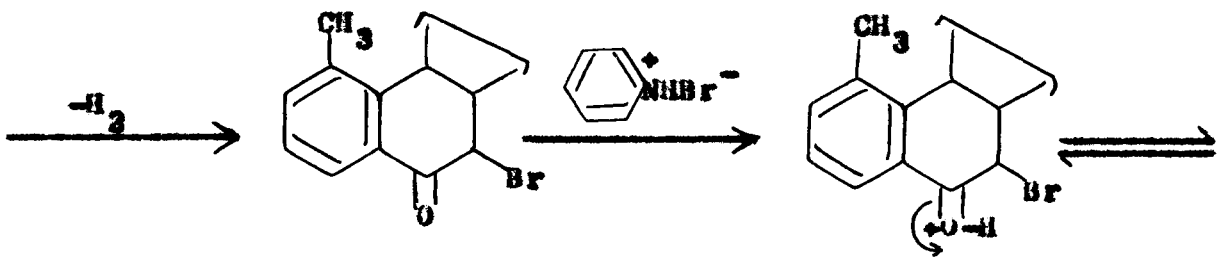
cationic intermediate formation in the conversion (CLXI) ⟶ (CLVI), and should involve an intermediate which has 3 potential sites of unsaturation in rings A and B.

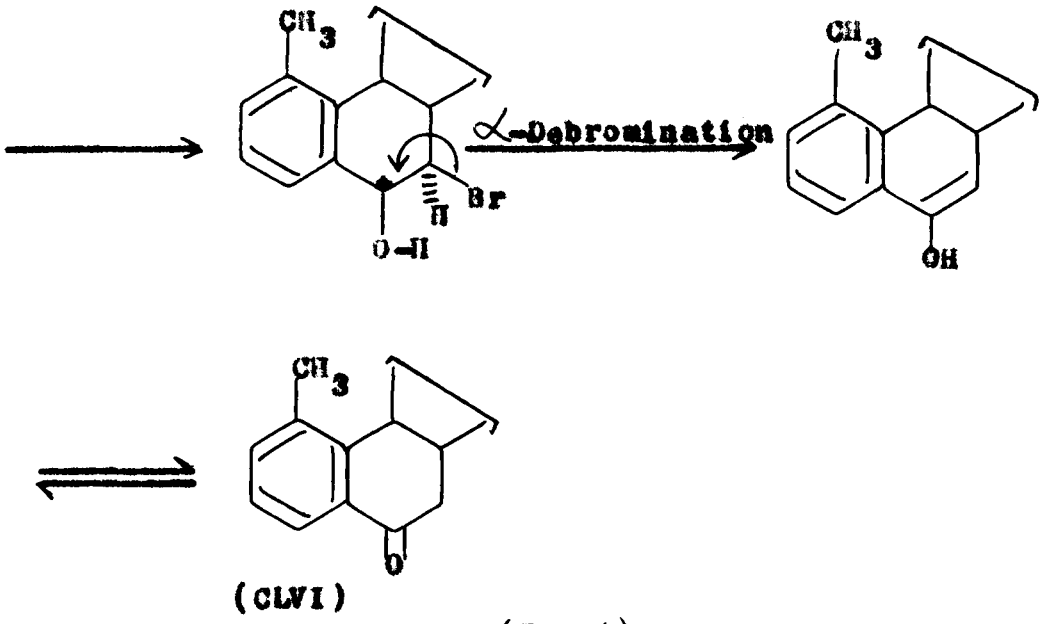
The following mechanism, though tentative is being proposed for the formation of ring A aromatised product (CLVI) from (CLXI).



(CLXI)



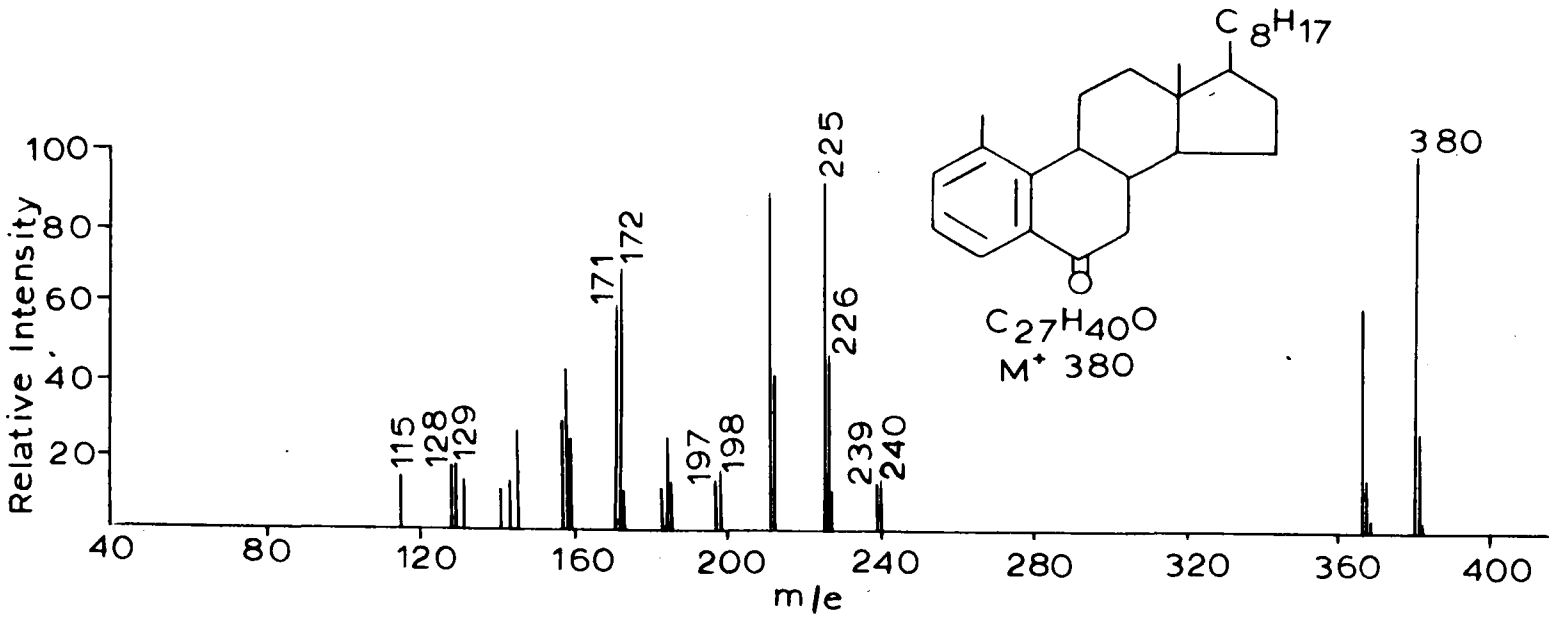




(CLVI)

(Fig.4)

The mass spectrum of (CLVI) gave molecular ion peak at m/e 380 ($C_{27}H_{40}O$), followed by other significant peaks at m/e 240, 239, 226, 225, 212, 211, 198, 197, 172, 171 and lower mass peaks. The mass spectrum of (CLVI) was found to be very similar to the one obtained for (CLXIII). However, there was no $M-CH_3$ or $M-C_8H_{17}$ (side chain) peak in the spectrum of (CLVI). Like (CLXIII), the mass spectrum of (CLVI) did not show the loss of CO from the molecular ion. On the basis of strong similarity in the mass spectra of (CLXIII) and (CLVI), the mechanism of the formation of individual fragment ions are not being repeated. However, the structure of various ions have been formulated by analogy in the following table 2.



Mass Spectrum of (CLVI) (Fig.-4)

Table - 2

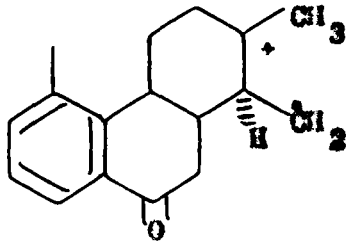
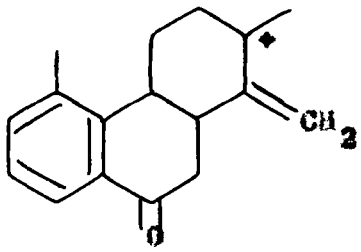
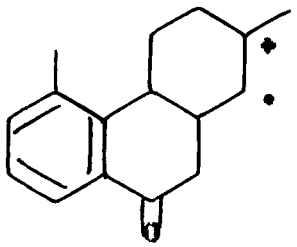
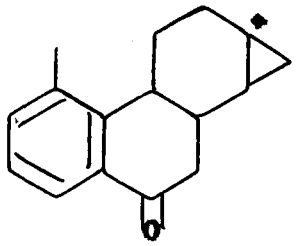
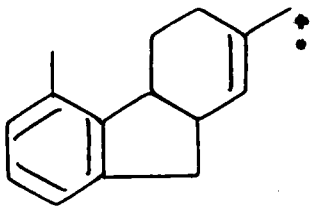
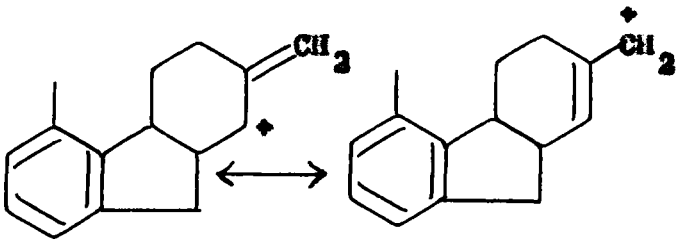
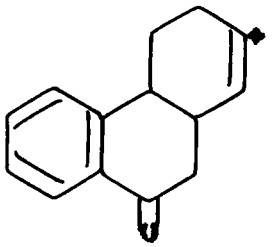
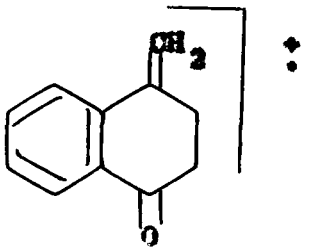
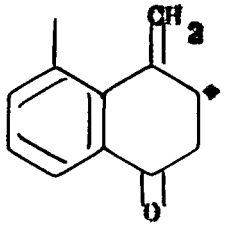
Fragments	m/e	Composition
	240	$C_{17}H_{20}O$
	239	$C_{17}H_{19}O$
	226	$C_{16}H_{18}O$
	225	$C_{16}H_{17}O$

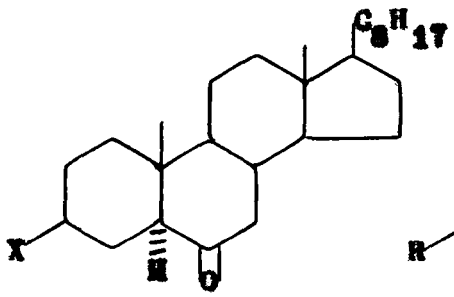
Table - 2 (Contd.)

Fragments	m/e	Composition
	198	$C_{15}H_{18}$
	197	$C_{15}H_{17}$
	211	$C_{15}H_{15}O$
	172	$C_{12}H_{12}O$
	171	$C_{12}H_{11}O$

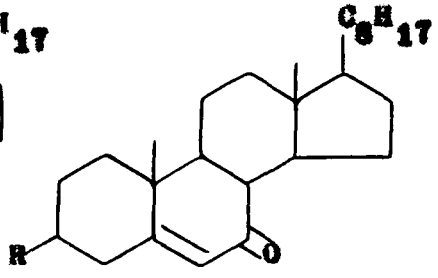
Azasteroids

The Beckmann rearrangement and Schmidt reaction of steroidal ketoximes and ketones, respectively, are the two most facile and widely employed methods for the preparation of azasteroids. An excellent review entitled "Synthesis of azasteroids using Beckmann rearrangement and Schmidt reaction" has appeared recently [121].

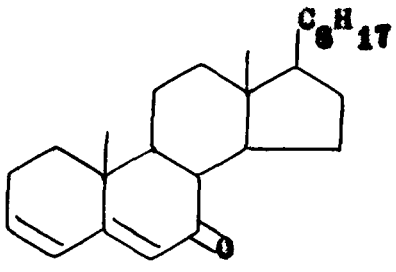
Several papers dealing with the preparation of azasteroids have appeared from these laboratories. These included azasteroids from 3β-halocholestan-6-ones (CLVIII, CLXV and CLXVI)[134-136], 3β-acetoxycholest-5-en-7-one (LXVIII)[147], cholest-5-en-7-one (CLXVII)[147], cholesta-3,5-dien-7-one (CXXXII)[169], cholesta-4,6-dien-3-one (CXVI)[145], 3β-acetoxycholest-4-en-6-one (CLXIV)[134], cholest-4-en-6-one (CLXVIII)[136], 3α,5-cyclo-5α-cholestan-6-one (CVII)[135], cholesta-2,4-dien-6-one (CXXXV)[150], 3α-cholestane-3,6-dione (CLVII)[170], and cholest-4-ene-3,6-dione (XXXVII)[170].



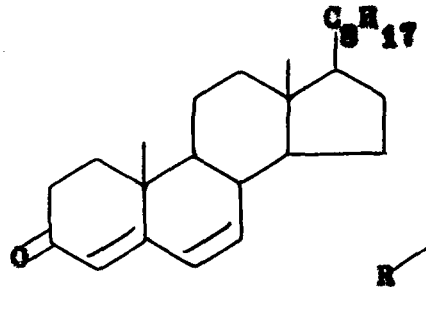
(CLVIII) X, Cl
(CLXV) X, Br
(CLXVI) X, I



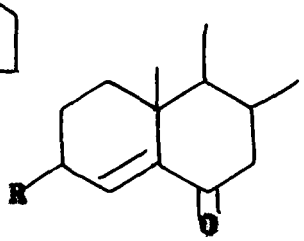
(LXVIII) R, OAc
(CLXVII) R, H



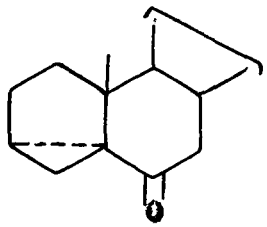
(CXXXII)



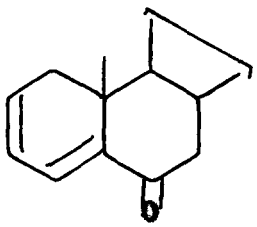
(CXXVI)



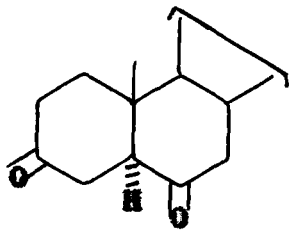
(CLXIV) R, OAc
(CLXXVIII) R, H



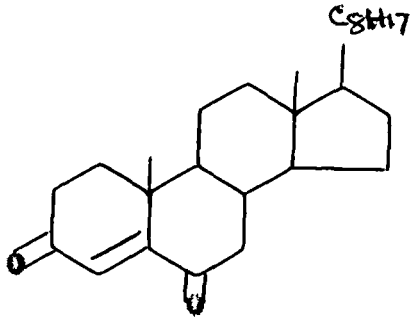
(CVII)



(CXXXV)

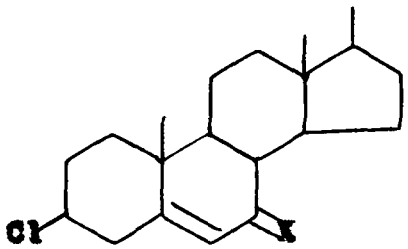


(CLVII)

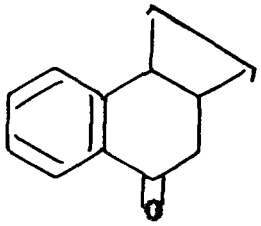


(XXXVII)

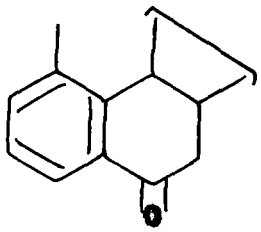
The present work is an extension of the above and employed the hitherto unexplored steroidal ketones, such as 3β-chlorocholest-5-en-7-one (CLXXIX), 19-norcholesta-1,3,5(10)-trien-6-one (CLXIII) and 1-methyl-19-norcholesta-1,3,5(10)-trien-6-one (CLVI).



(CLXXIX) X, O
(CLXXX) X, N-OH



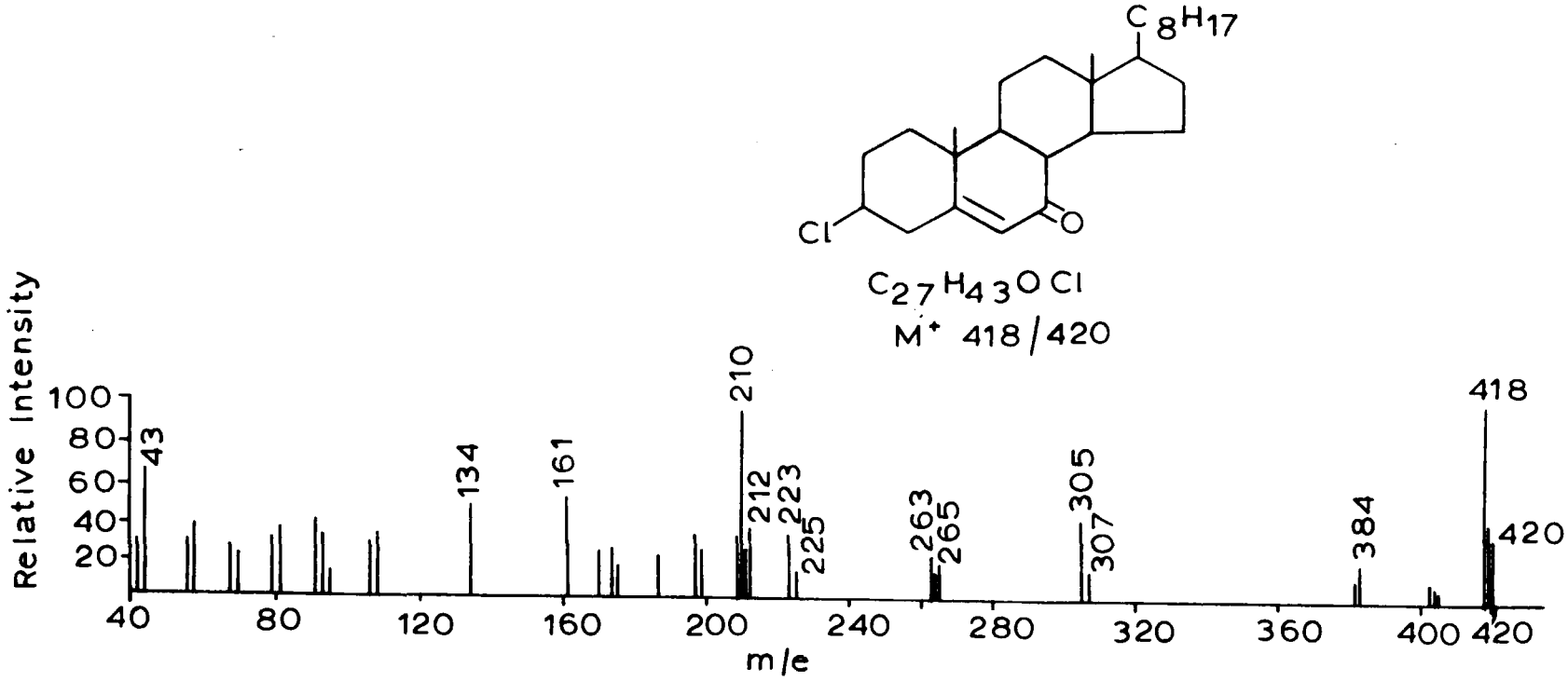
(CLXIII)



(CLVI)

Beckmann rearrangement of 3β-chlorocholest-5-en-7-one oxime (CLXXX); 3β-Chloro-7a-aza-8-homocholest-5-en-7-one (CLXXXI)

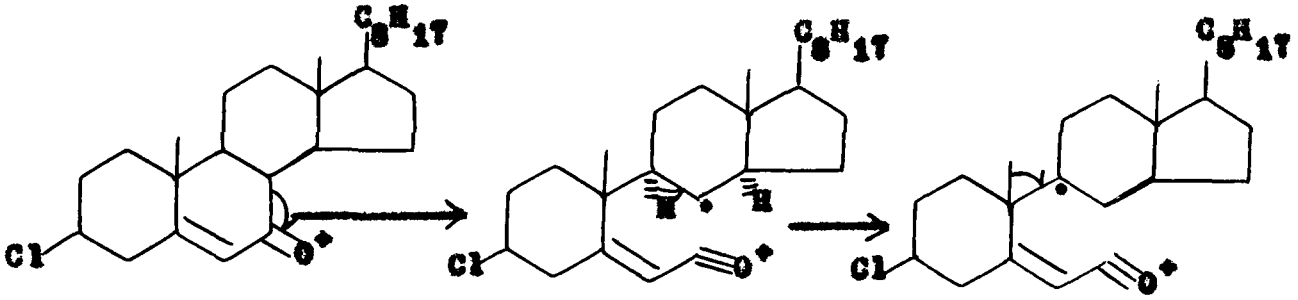
3β-Chlorocholest-5-en-7-one (CLXXIX) was prepared according to the literature procedure[171]. Its i.r. spectrum showed bands at 3030w (C=C-H), 1675 (C=C-C=O), 1635 (C=C-C=O), and 768 cm^{-1}(C-Cl)[155]. The u.v. spectrum of (CLXXIX) gave absorption maxima at 243 nm which further supported the presence of an α,β-unsaturated carbonyl chromophore. The n.m.r. spectrum gave signals at δ 5.38s (1H, C6-H, vinylic proton), 3.96br (1H, $W_{\frac{1}{2}}$ 20 Hz, α-oriented, axial, C3-H), 1.25s (3H, C10-CH_3), 0.70 (C13-CH_3), 0.83 and 0.93 (other methyl protons). The mass spectrum of the compound (CLXXIX) (Fig. 5) gave molecular ion peak at m/e 418/420 ($C_{27}H_{43}OCl$) along with other ion peaks at m/e 403/405 (M-CH_3), m/e 305/307 (M-C_8H_{17}), m/e 269, m/e 323/325, m/e 210/212, m/e 199, m/e 197, m/e 174, m/e 161, m/e 134, m/e 107, m/e 105 and lower mass peaks. The presence of chlorine facilitated the analysis of the spectrum because of its isotopes in the ratio of 1:3 (mass 35 and 37). The formation of some of the fragment ions has been shown according to the following schemes (Scheme 14-17).



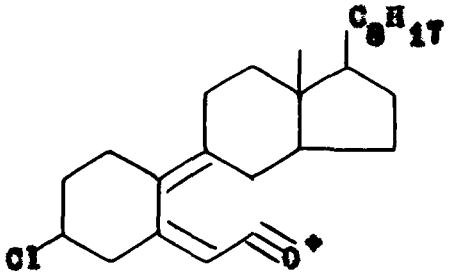
Mass Spectrum of (CLXXIX) (Fig.-5)

Scheme - 14

m/e 403/405 ($M-CH_3$)



(CLXXIX')

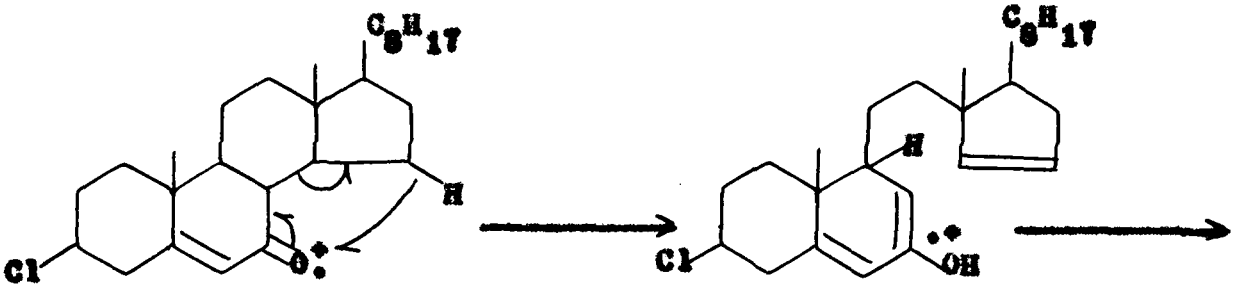


(V)

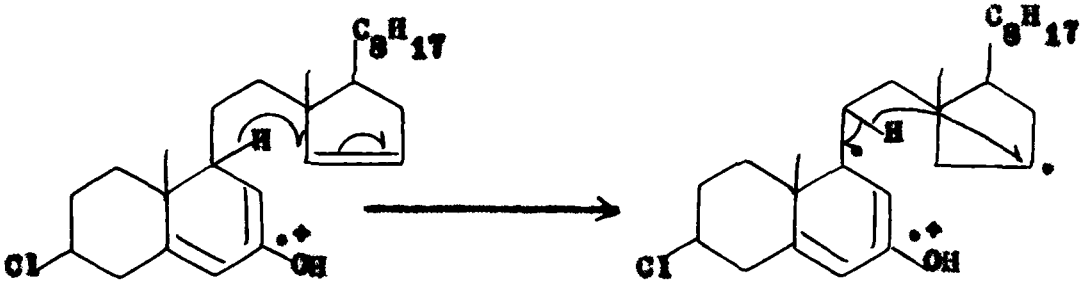
m/e 403/405 $C_{26}H_{44}OCl$

Scheme - 15

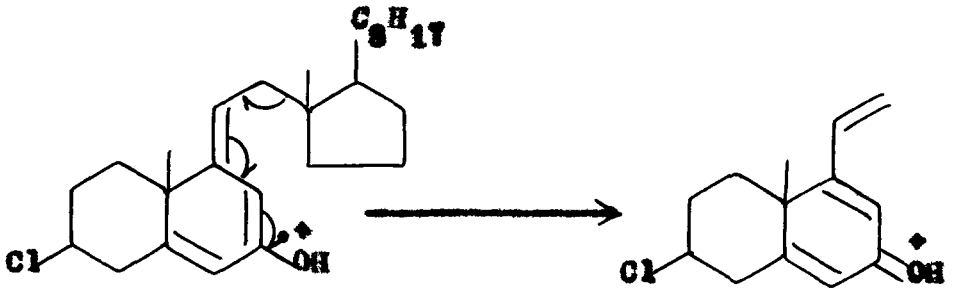
m/e 223/225



(CLXXIX')



(w)

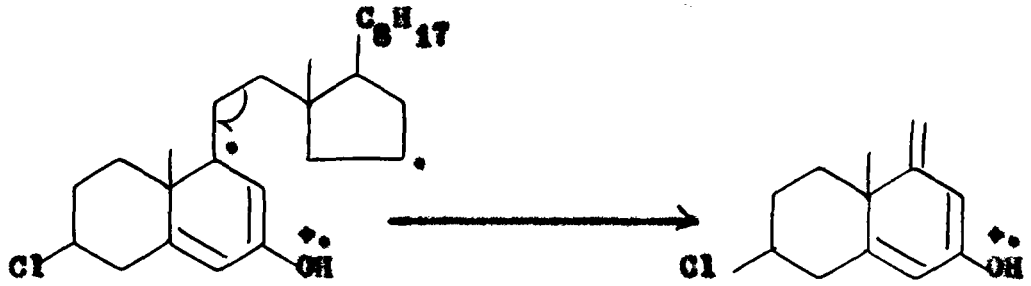


(x)

m/e 223/225 $C_{13}H_{16}OCl$

Scheme - 16

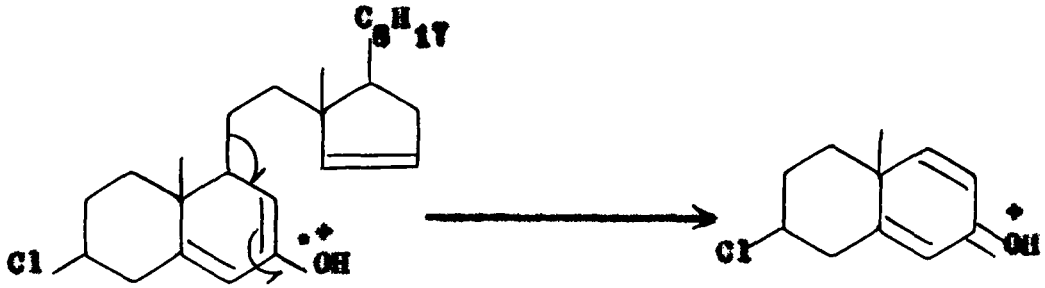
m/e 210/212



(w)

(y)
m/e 210/212 $C_{13}H_{15}OCl$

m/e 197



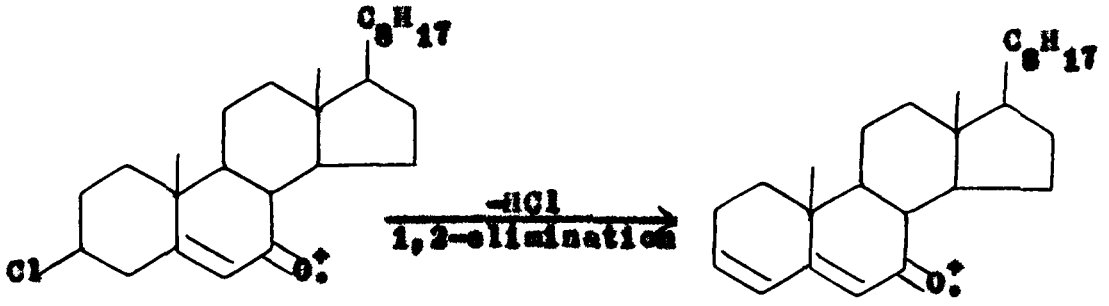
(z)
m/e 197 $C_{11}H_{14}OCl$

m/e 187, m/e 174 and m/e 161

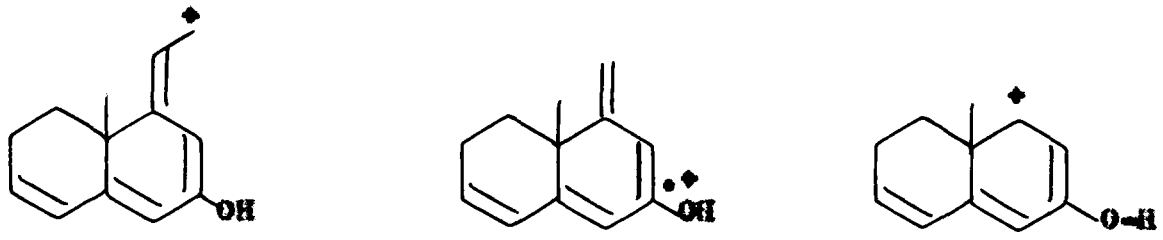
As expected the molecular ion (CLXXIA') loses HCl to give fragment ion (g). The loss of HCl from chlorides usually involves,

1,4, 1,3, elimination[172]. However in this case it is reasonable to assume that the loss occurs by 1,2-elimination thus giving rise to a more conjugated species (g)[173].

The fragment ions m/e 197 (b), m/e 174 (c) and m/e 161 (d) from (CLXXIX') correspond to m/e 223/225 (x), m/e 210/212 (y) and m/e 197 (z) and therefore are formulated as shown below.



(CLXXIX') (g)



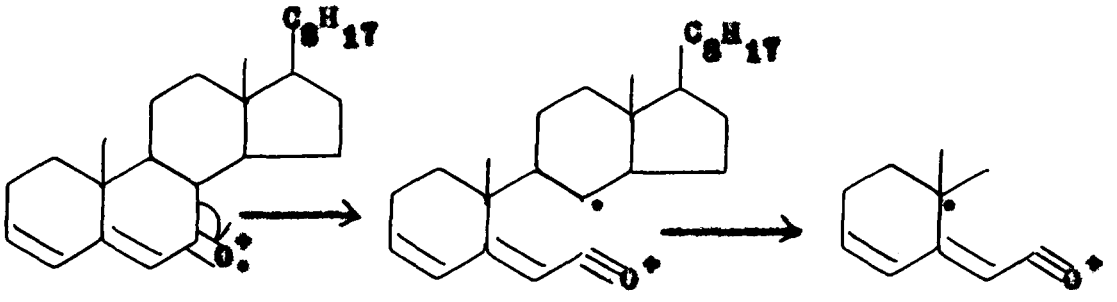
m/e 197 (b) ($C_{13}H_{17}O$) m/e 174 (c) ($C_{12}H_{14}O$) m/e 161 (d) ($C_{11}H_{13}O$)

<u>m/e 134 and m/e 269</u>

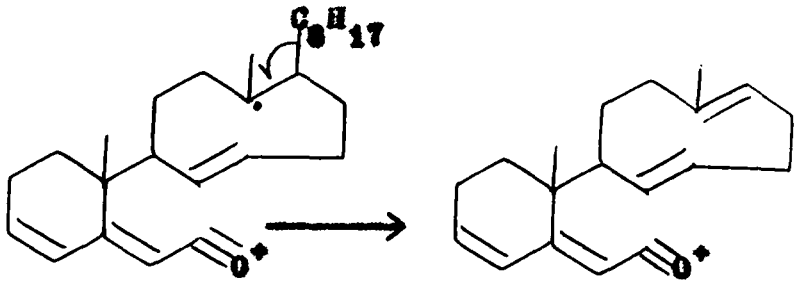
The formation of these ions is expected on the basis of α-cleavage as observed in other ketones[174,175]. The first cleavage

involving C7-8 bond in the ion (CLXXIX') gives the CS radical species (e) which has three suitably situated bonds for further cleavage and they may lead to different fragment ions as shown in scheme (Scheme 17).

Scheme - 17



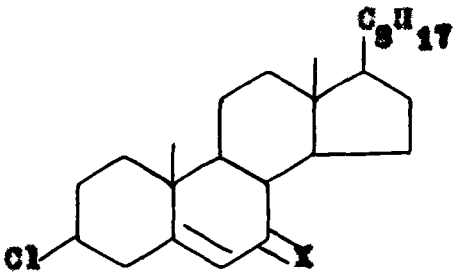
(a) (e) (f) m/e 134 ($C_9H_{10}O$)



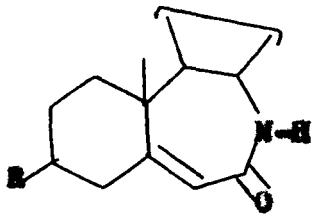
(g) m/e 269 ($C_{19}H_{25}O$)

The corresponding oxime (CLXXX), m.p. 197° was prepared from (CLXXIX) by usual method. The oxime (CLXXX) analysed for $C_{27}H_{44}NOCl$ (positive Beilstein test). Its i.r. spectrum displayed bands at 3294s (N-O<u>H</u>), 1645w (C=N-), 1620w (C=C), and 768 cm^{-1} (C-Cl)[155]. The n.m.r. spectrum gave signals at δ 7.99br (1H, disappeared on addition of D_2O, N-O<u>H</u>), 6.76s (1H, C6-<u>H</u>, vinylic proton)[175,176], 3.85br (1H, $W\frac{1}{2}$ 22 Hz, α-oriented, C3-<u>H</u>, axial)[157], 2.85 dist.d (2H, C4-<u>H</u>$_2$), 1.15s (3H, C10-C<u>H</u>$_3$), 0.71s (3H, C13-C<u>H</u>$_3$), 1.0, 0.91 and 0.83 (other methyl protons).

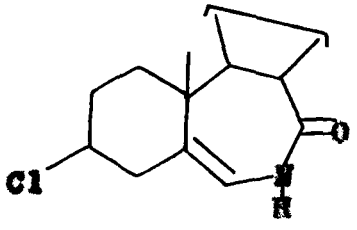
The homogeneity of the oxime (CLXXX) was assured by t.l.c. in different solvent systems and by repeated crystallisation.



(CLXXIX) R,Cl; X,O
(CLXXX) R,Cl; X, N-OH



(CLXXXI) R, Cl
(CLXXXII) R, H



(CLXXXIII)

The Beckmann rearrangement of the oxime (CLXXX) with thionyl chloride followed by alkali treatment furnished a single lactam (CLXXXI), m.p. 170-171°. The lactam (CLXXXI) analysed for $C_{27}H_{44}NOCl$ (positive Beilstein test). The chlorolactam, m.p. 170-171° can be formulated either as (CLXXXI) or its isomer, 3β-chloro-7-aza-B-homocholest-5-en-7a-one (CLXXXIII). Evidence in support of the structure (CLXXXI) was obtained by spectral properties and chemical transformation.

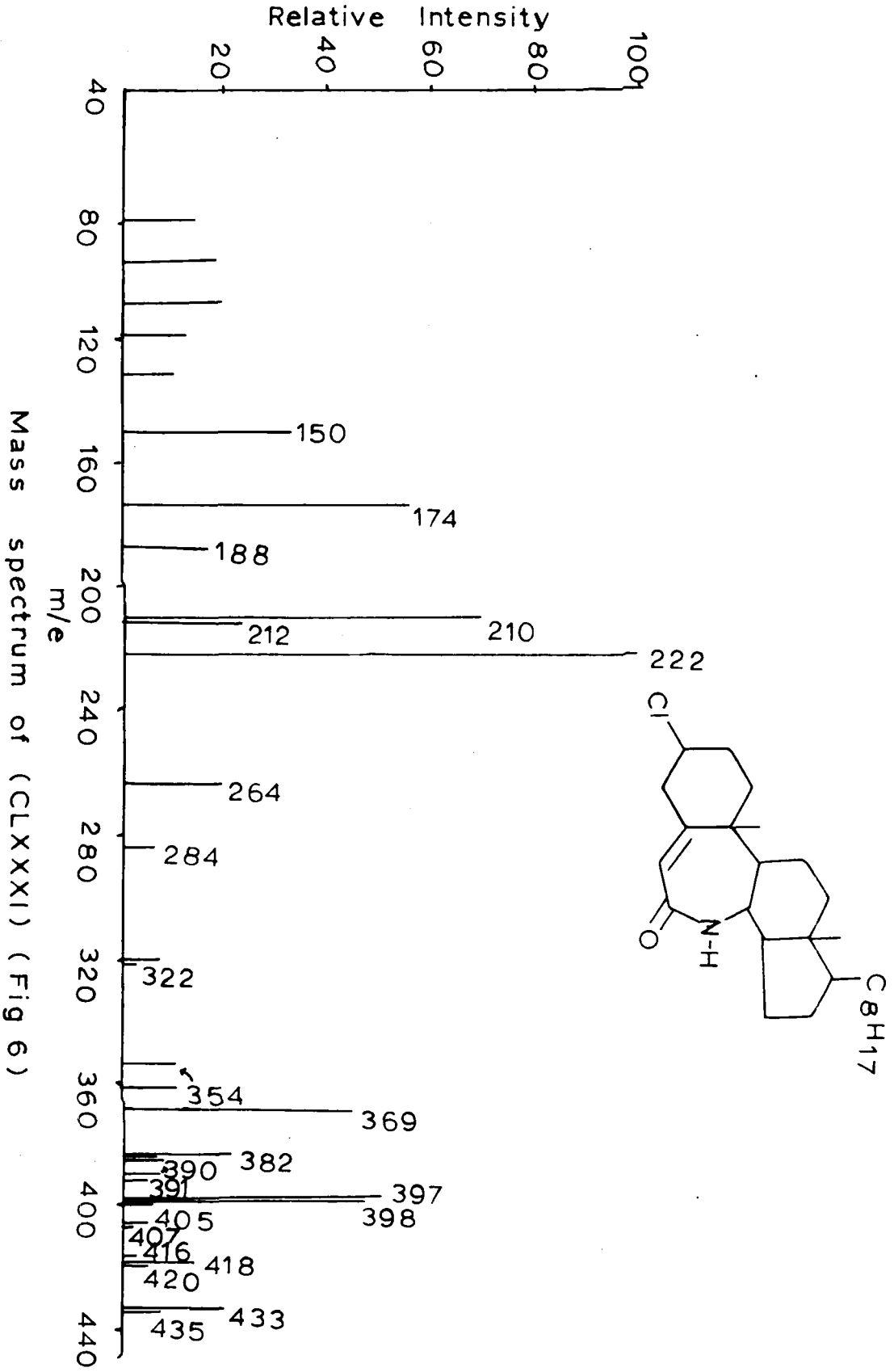
The u.v. spectrum of the lactam, m.p. 170-171° showed absorption maxima at 219 nm (∈ 4.3) which indicated that it contains the chromophore (C=C-C=O) as in (CLXXXI); the alternative structure (CLXXXIII) was likely to show absorption maxima at about 240 nm[131,177]. The i.r. spectrum gave bands at 3290, 3240, 3190 (N-H), 1665 (C=C-C-NH), and 1624 cm^{-1} (C=C). The n.m.r. spectrum gave signals at δ 6.25br (1H, disappeared on addition of D_2O; CO-NH), 5.95s (1H, C6-H, vinylic proton), 3.9br (1H, $W_{\frac{1}{2}}$ 22 Hz, C3-H, ∝-oriented, axial)[157], 3.3m (1H, C9-H), 2.3m (2H, C4-H), 1.49s (3H, C10-CH_3), 0.70s (C13-CH_3), 0.93, and 0.85 (other methyl protons). After D_2O shake the signal at δ 3.3 (C3-H), was simplified; the other parts of the spectrum (excepting for the disappearance of the signal at δ 6.25 (CONH), remained unchanged. The appearance of a vinylic proton signal at δ 5.95 as a singlet further supported the structure (CLXXXI).

The same lactam (CLXXXI) was also obtained from the oxime (CLXXX) when the latter was treated with p-toluenesulphonyl chloride in pyridine, followed by column chromatography over alumina.

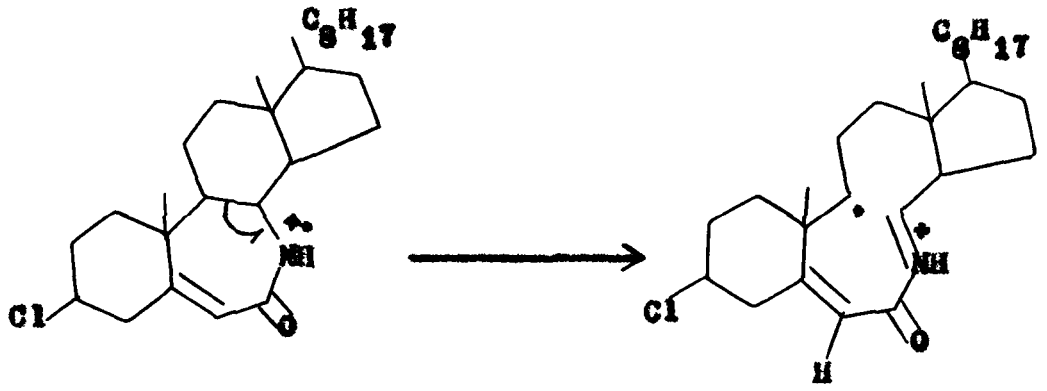
The chemical evidence in support of the structure (CLXXXI) was obtained by converting it to the known lactam, 7a-aza-D-homocholest-5-en-7-one (CLXXXII)[147], m.p. and m.m.p. 210-211° by sodium amyl alcohol reduction of the chlorolactam (CLXXXI).

(CLXXXI) (CLXXXII)

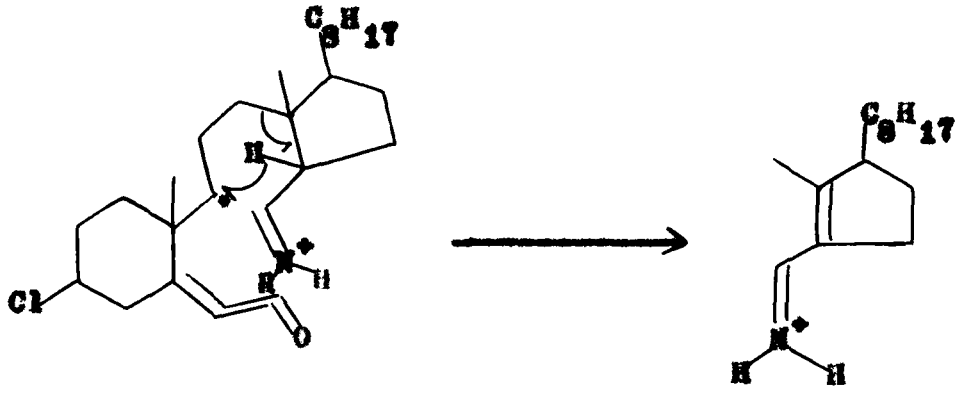
Further evidence in support of the chlorolactam (CLXXXI) was obtained by mass spectral studies. The mass spectrum of (CLXXXI) (Fig. 6) gave molecular ion peak at 433/435 (1:3) ($C_{27}H_{44}NOCl$) with base peak at m/e 222 ($C_{15}H_{28}N$). The appearance of strong peak at m/e 222 ($C_{15}H_{28}N$) has been established as diagnostic value in the characterisation of 7a-aza-steroids in the cholestane series[178]. The formation of the fragment ion m/e 222 ($C_{15}H_{28}N$) has been rationalised according to the following mechanism.



Mass spectrum of (CLXXXI) (Fig 6)



(CLXXXI')



m/e 322 ($C_{15}H_{28}N$)

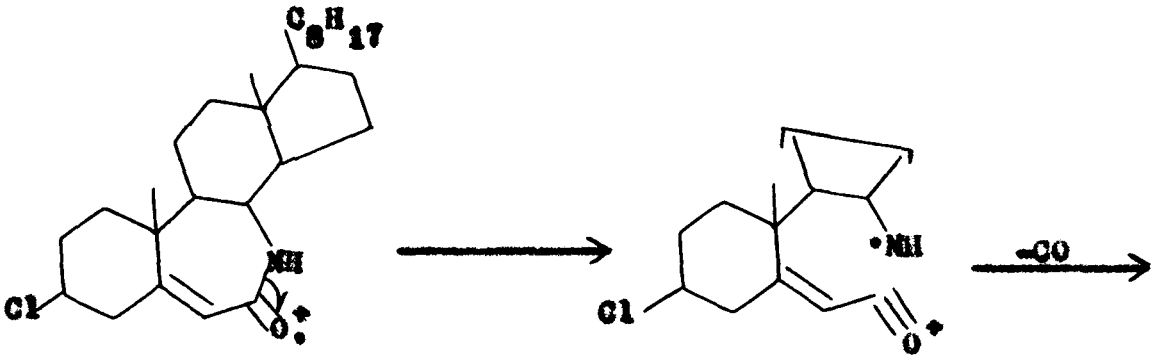
The other significant peaks in the mass spectrum were observed at m/e 418, m/e 420 (M-CH_3), 405, 407 (M-CO), 398 (M-Cl), 397 (M-HCl), 392, 390 (M-CH_3 and CO), 383 (M-Cl, -CH_3), 382 (m/e 397-CH_3), 369 (m/e 397-CO), 354 (m/e 369-CH_3), 322 (M-C_8H_{13}), 284, 264, 213, 210, m/e 188, 174, 150 and lower mass peaks. The formation of some of the salient fragment ions has been shown in the following schemes (Scheme 17-20).

<u>m/e 405 and m/e 407</u> (1:3)

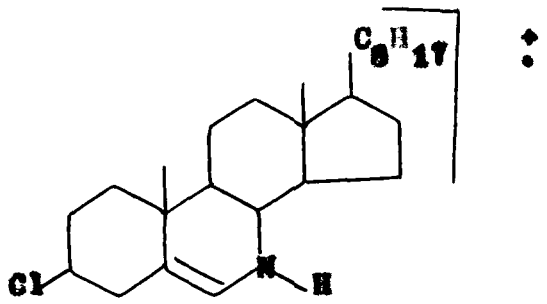
These peaks are relatively weak and represent the loss of CO from the molecular ion. Since the loss of CO involves the

cleavage of a vinylic bond which is a less favourable cleavage, at one stage or the other, these peaks, as expected are weak.

Scheme - 17



(CLXXXI')



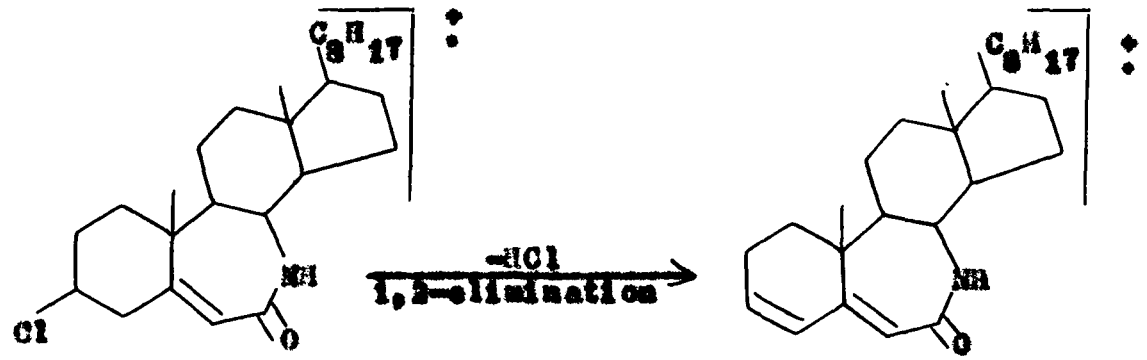
m/e 407/405

m/e 398

This fragment ion peak is fairly strong and represents the loss of chlorine from the molecular ion. This assumption is further supported by a metastable peak at m/e 365.8.

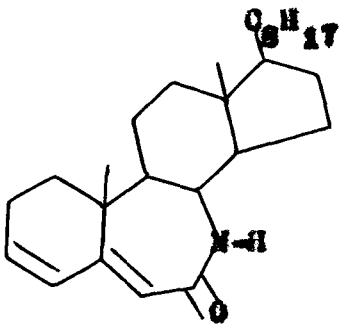
m/e 397

As expected the molecular ion looses HCl to give this fragment ion and this is supported by metastable peak at m/e 354. The loss of HCl from chlorides usually involves, 1,4 and 1,3-elimination[172,173]. However, in this case it is reasonable to suppose that the loss occurs by 1,2-elimination thus giving rise to a more conjugated species[173].



(CLXXXI') (h) m/e 397

There is considerable support in this formulation since (h) (m/e 397) represents the molecular ion of the lactam, 7a-aza-B-homocholesta-3,5-dien-7-one (CLXXXIIIa) and some of the important ion peaks are comparable with those observed in the mass spectrum of (CLXXXIII-a) For example, fragment ion m/e 188, m/e 174 and

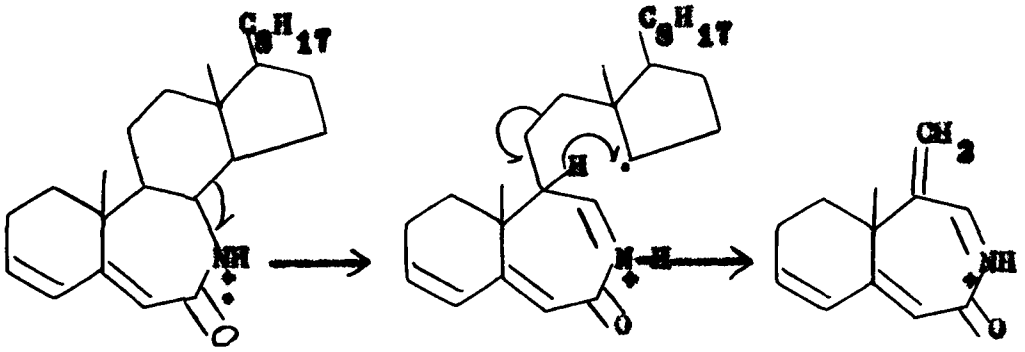


(CLXXXIII-a)

m/e 150 seems to have their origin from m/e 397 (h). These have been formulated by analogy in Scheme 18.

Scheme - 18

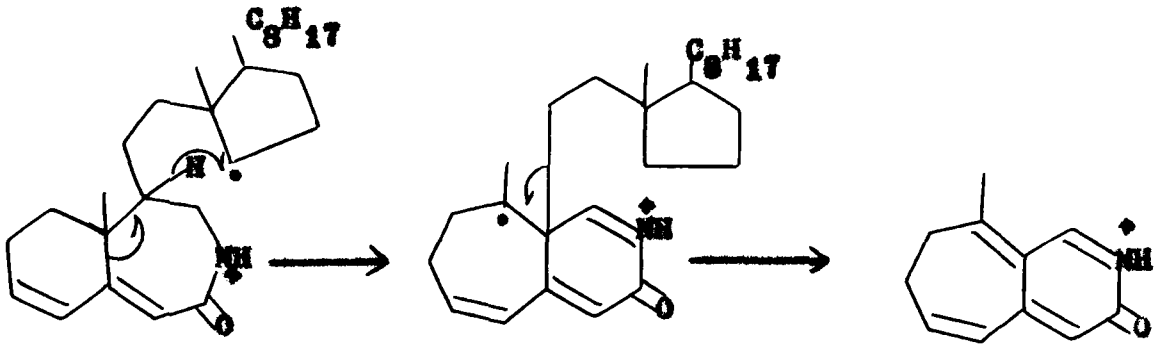
m/e 188



(h) m/e 397 (i) (j) m/e 188 ($C_{12}H_{14}NO$)

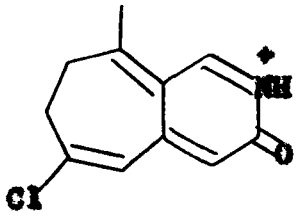
Scheme - 19

m/e 174



(k) m/e 174 ($C_{11}H_{12}NO$)

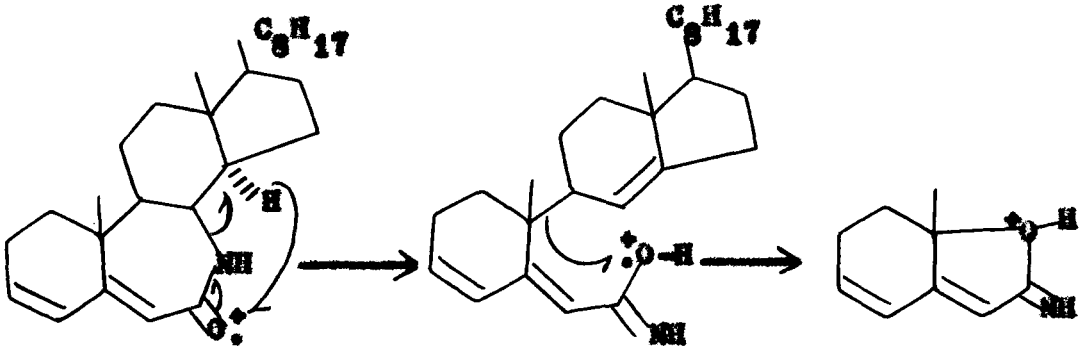
The chlorine containing fragment ion peak at m/e 210/212, thus can be formulated as (l).



(1)
m/e 210/212

Scheme - 20

m/e 150



(h)
m/e 397

(m)
m/e 150 ($C_9H_{12}NO$)

The Schmidt reaction of the ketone (CLXXIX) with sodium azide and polyphosphoric acid also gave the same lactam (CLXXXI) as the sole isolable nitrogen containing product.

Schmidt reaction of 19-norcholesta-1,3,5(10)-trien-6-one(CLXIII); 6-aza-8-homo-19-norcholesta-1,3,5(10)-trien-7-one (CLXXXIV)

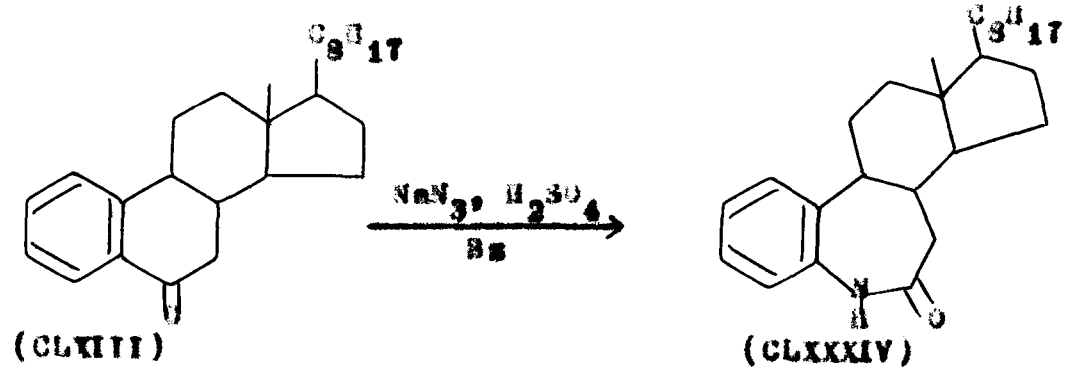
The Schmidt reaction (CLXIII) was attempted in two ways.

A. **In polyphosphoric acid**

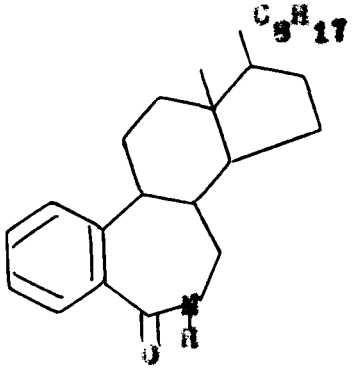
The ketone (CLXIII), on treatment with equimolar quantity of sodium azide in polyphosphoric acid (50-60°) for 8 hours, did not undergo the expected Schmidt reaction and the unreacted ketone was recovered quantitatively.

B. **In conc. sulphuric acid**

The Schmidt reaction of the ketone (CLXIII) was successfully carried out with sodium azide and conc. sulphuric acid in benzene solvent. It gave a single lactam (CLXXXIV), m.p. 98°. Its homogeneity was assured by repeated crystallization and t.l.c. in different solvent systems. The lactam (CLXXXIV) analysed for $C_{26}H_{39}NO$. Its i.r. spectrum gave bands at 3230, 3150(NH), 1670 (CONH), 1645 and 1580 cm^{-1} (C=C of benzenoid ring system)[155]. These values are also compatible with the isomeric lactam, 7-aza-8-homo-19-norcholesta-1,3,5(10)-trien-6-one (CLXXXV).



(CLXIII) (CLXXXIV)



(CLXXXV)

The u.v. spectrum of the lactam (CLXXXIV) gave absorption maxima at 239 nm. However, a distinction between the two isomeric lactams (CLXXXIV) and (CLXXXV) was obtained by n.m.r. spectrum of the compound. The n.m.r. spectrum gave signals at δ 10.0s (1H, disappeared on addition of D_2O; CONH), 7.11br,s (4H, aromatic protons, C1-H, C2-H, C3-H and C4-H), 2.2m (2H, C7a-H_2)[157], 0.71s (3H, C13-CH_3), 0.81 and 0.88 (other methyl protons). These values firmly support the structure (CLXXXIV). After deuterium exchange, there was no change in any part of the spectrum (excepting the disappearance of CONH signal at δ 10.0). The alternative structure (CLXXXV) was expected to give a multiplet for NH proton (CONH-CH_2). Further, a signal for 2 protons was expected in the region around δ 3.5 for CONH-CH_2, which would have been simplified after deuterium exchange.

The mass spectrum of 19-nor-6-aza-B-homocholesta-1,3,5(10)-trien-7-one (CLXXXIV)(Fig. 7) gave molecular ion peak at m/e 381 ($C_{26}H_{39}NO$) along with other important peaks at m/e 366, 353, 338, 279, 226, 184, 173, 172, 167, 146, 145, 144, 130, 120, 119 and lower mass peaks. The formation of significant ions can be rationalised according to schemes given below. The fragmentation pathways suggested are supported by accurate mass measurement of some of the salient fragment ions. The mechanistic schemes suggested are tentative in the absence of mass spectra of appropriate deuterated analogues of (CLXXXIV).

m/e 366

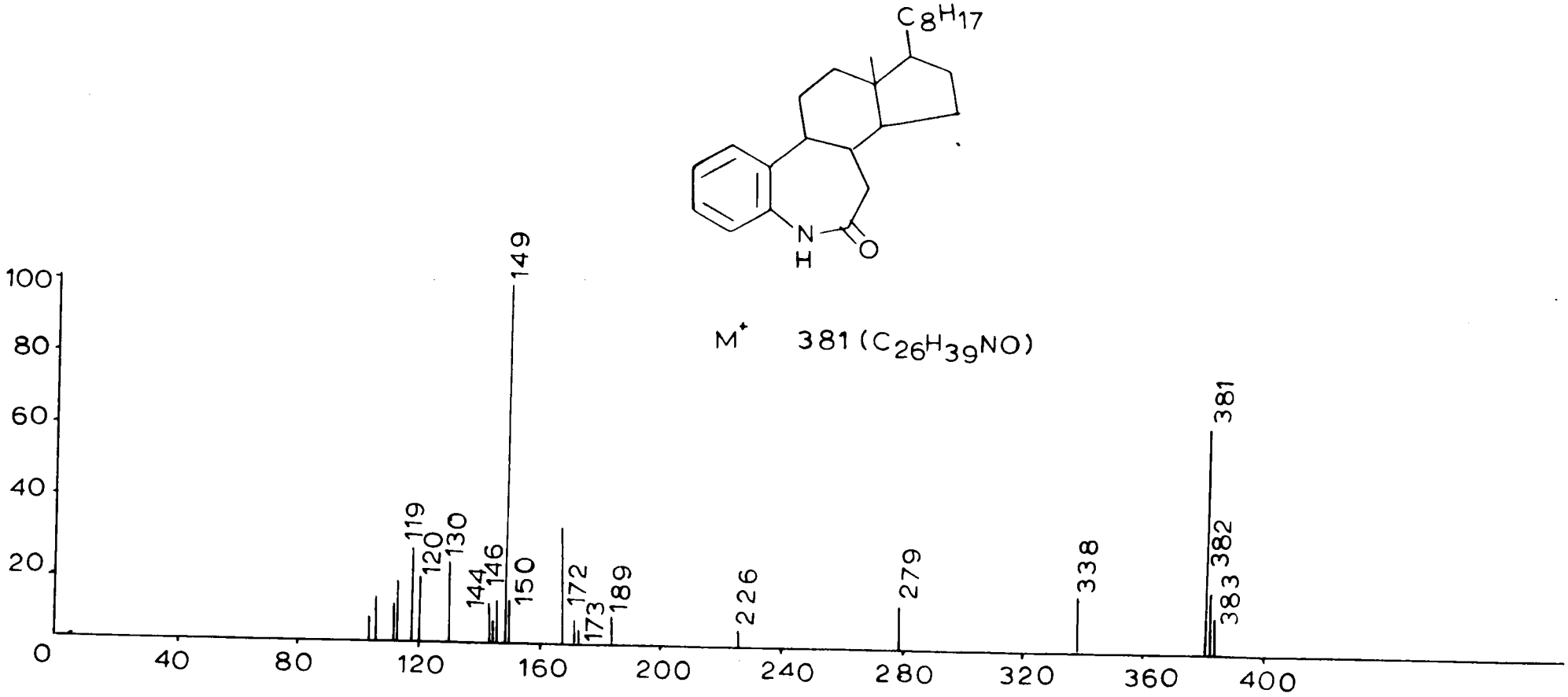
This fragment ion obviously results by the loss of a methyl group from the molecular ion.

m/e 353

As expected the loss of CO occurred from the molecular ion to give the ion m/e 353.

m/e 338

This fragment ion represents the loss of mass unit 43 from the molecular ion, conveniently it can be shown to arise by the loss of CO from the ion m/e 366 or by the loss of a methyl group from the ion m/e 353.

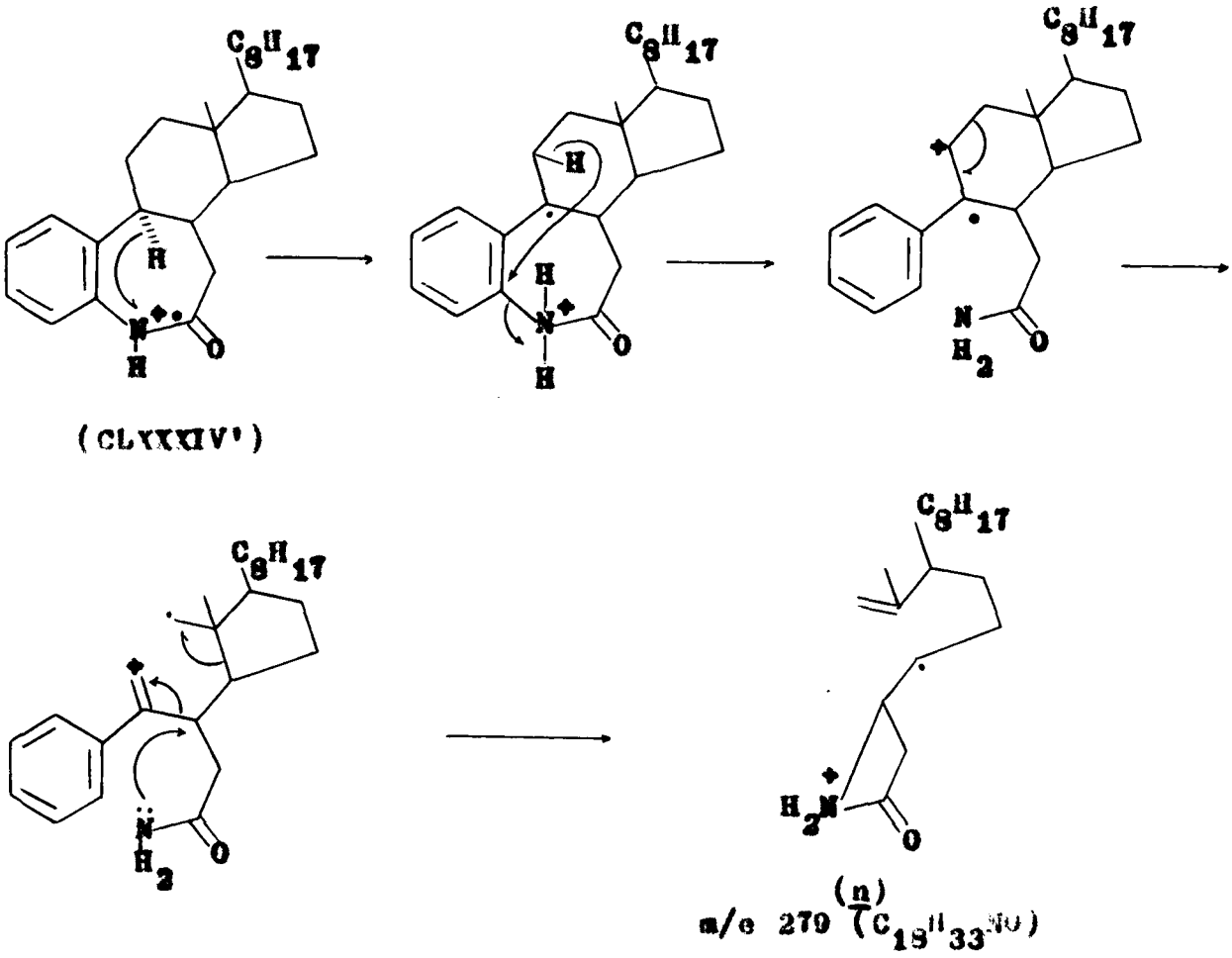


Mass spectrum of (CLXXXIV) (Fig 7)

m/e 279

This fragment ion results by the loss of mass unit 102 from the molecular ion. The accurate mass measurement showed the composition $C_{18}H_{33}NO$. One of the possibilities of the formation of the ion ($C_{18}H_{33}NO$) can be shown according to Scheme 21.

Scheme - 21

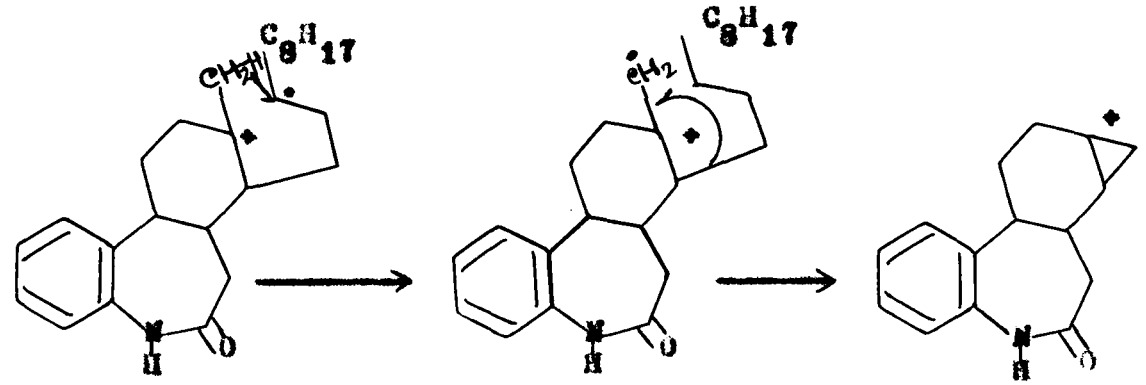


m/e 226

This fragment ion results by hydrocarbon-directed

fragmentation which involves the loss of ring D and the side chain. The pathway has been depicted in Scheme 22.

Scheme - 22



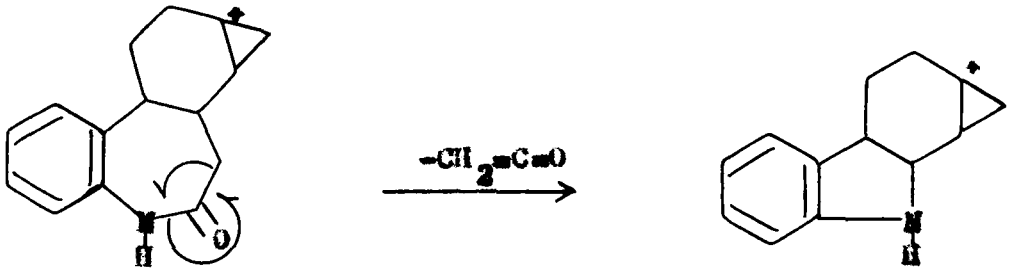
(CLXXXIV[m])

m/e 226 (o) ($C_{15}H_{16}NO$)

m/e 184

The genesis of the fragment ion m/e 184 ($C_{13}H_{14}N$) can be shown according to Scheme 23, where the loss of a molecule of ketene from the ion m/e 226 (o) is involved. Interestingly the loss of a ketene molecule does not occur from the molecular ion, though the latter is quite capable of doing so.

Scheme - 23



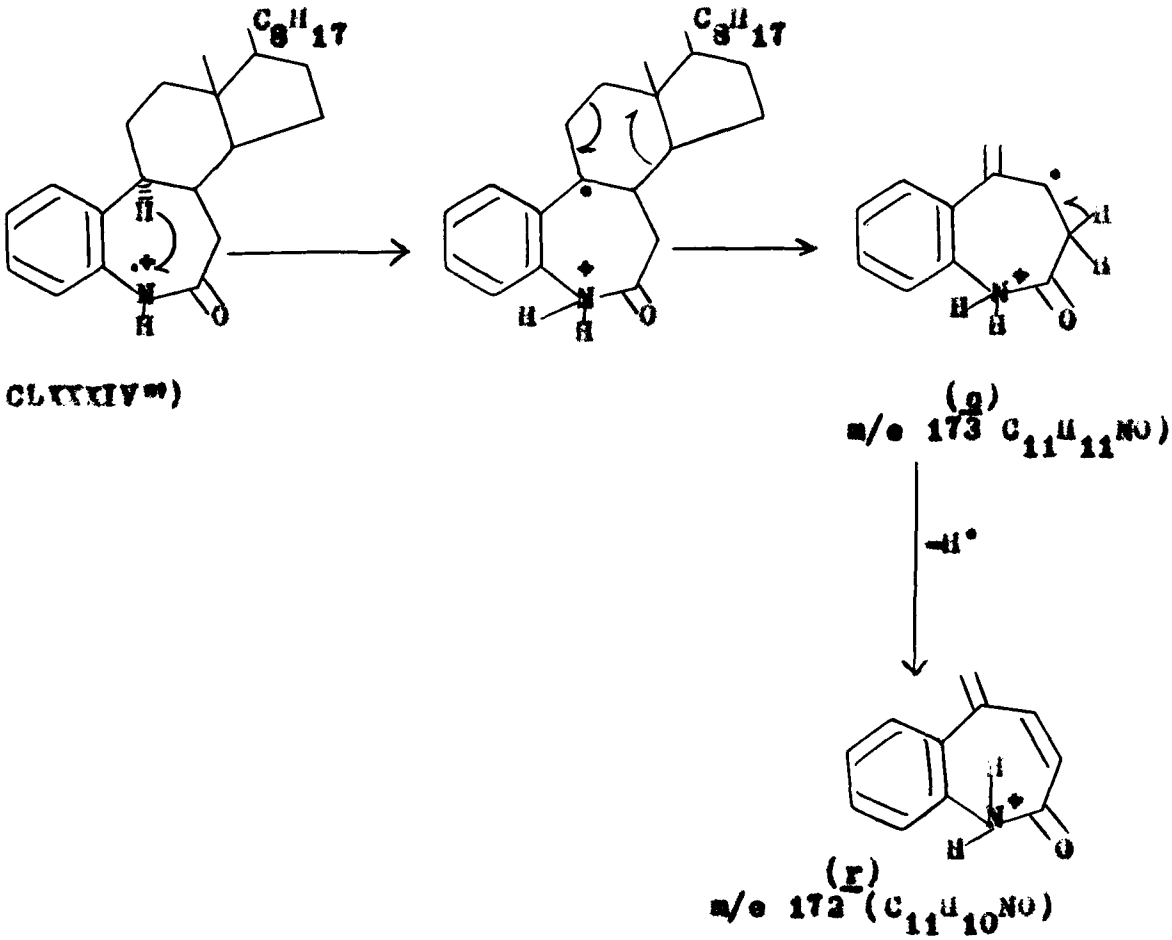
m/e 226 (o)

m/e 184 (p) ($C_{13}H_{14}N$)

m/e 173 and 172

From their compositions ($C_{11}H_{11}NO$ and $C_{11}H_{10}NO$), it is evident that these species consist of rings A, and B and C_{11}. A possible pathway for their formation is outlined in Scheme 24.

Scheme - 24

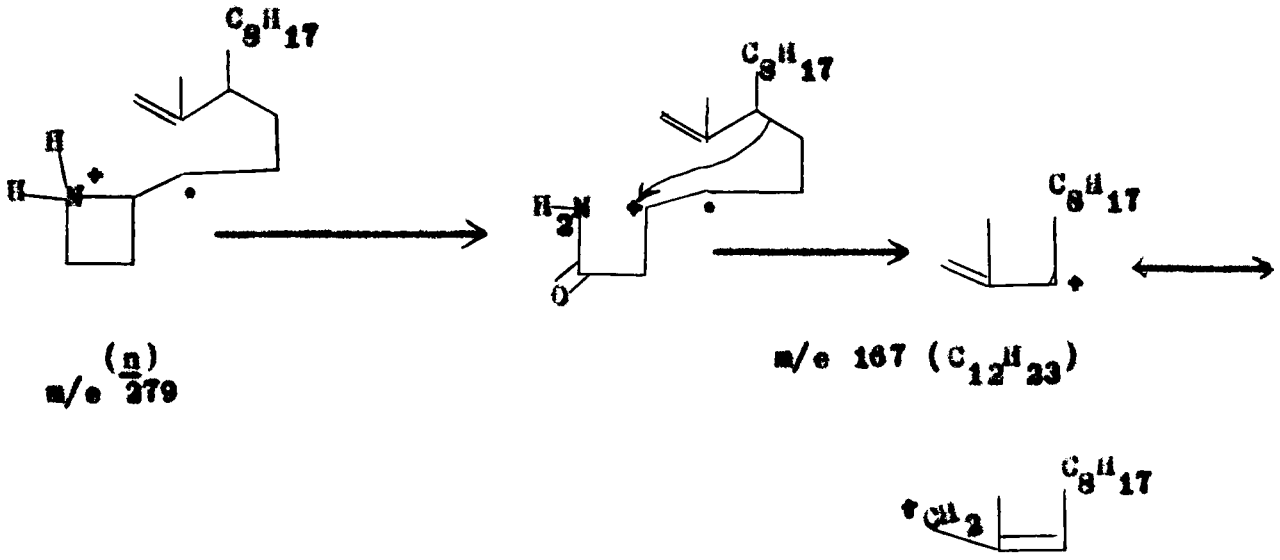


m/e 167

This fragment ion is a hydrocarbon species as revealed by accurate mass measurement ($C_{12}H_{23}$). Such an assembly of

carbon and hydrogen can only be conceived as arising out of the side chain and C_{12}, C_{13}, C_{17} and C_{18}. Probably this ion arises from the fragment ion m/e 279 (n) Scheme 25.

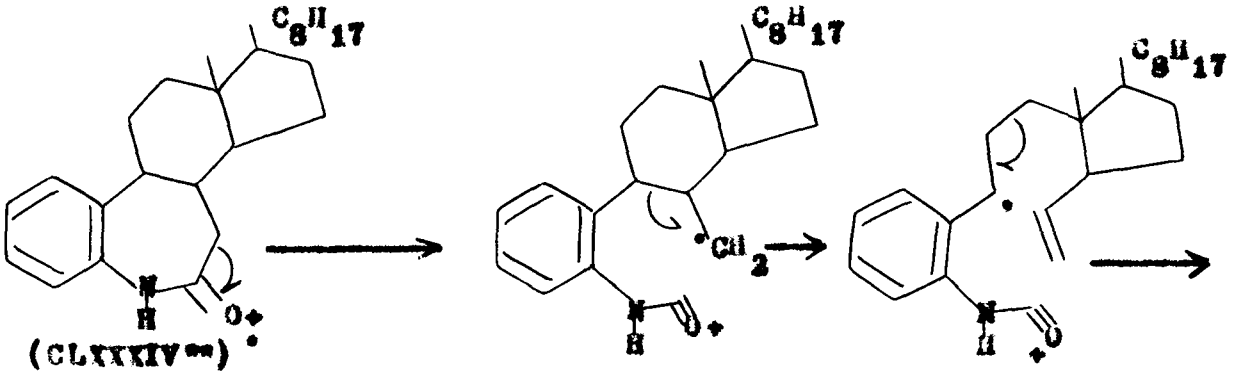
Scheme - 25

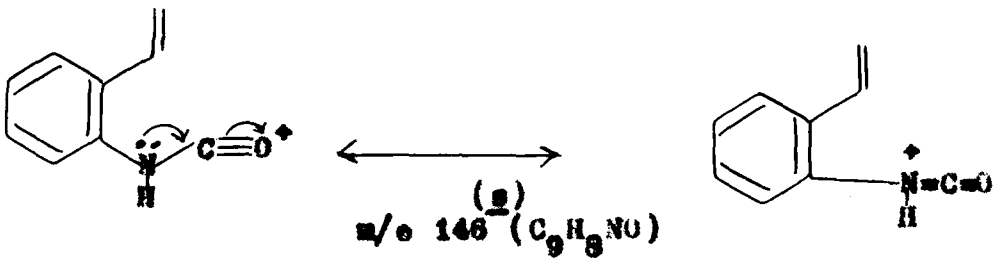


m/e 146

This fragment ion probably results by oxygen directed fragmentation of the molecular ion. In keeping the composition (C_9H_8NO) in view the following mechanism is being proposed for its formation (Scheme 26).

Scheme - 26

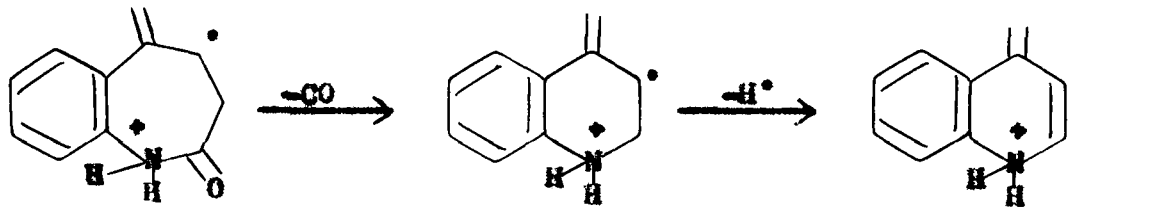




m/e 145 and 144

The accurate mass measurement of these ions showed the compositions $C_{10}H_{11}N$ and $C_{10}H_{10}N$, respectively. Apparently, the ion m/e 145 (t) results by the loss of CO from the fragment ion m/e 173 (g) and subsequent loss of hydrogen will produce the ion m/e 144 (u).

Scheme - 27

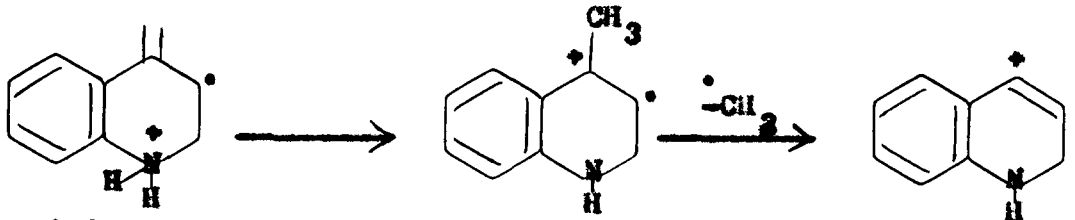


(s) m/e 173 (t) m/e 145 ($C_{10}H_{11}N$) (u) m/e 144 ($C_{10}H_{10}N$)

m/e 130

This fragment ion can arise either by the loss of a methyl group from the ion m/e 145 (t) or by a methylene loss from m/e 144 (u). This assumption finds support by the composition of the ion (C_9H_8N). An attempt has been made to rationalize the formation of this ion by the loss of a methyl group from the fragment ion m/e 145(t).

Scheme - 28

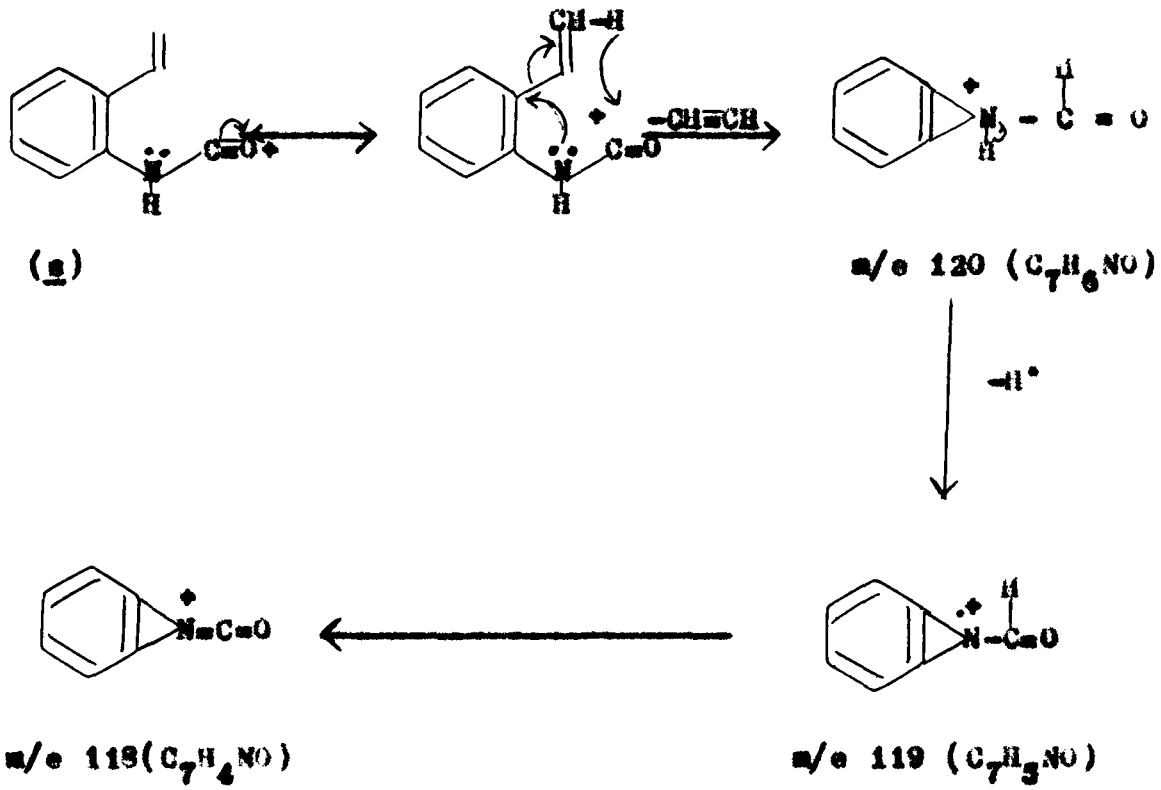


(t) m/e 145 (v) m/e 130 (C_9H_8N)

m/e 120, m/e 119 and m/e 118

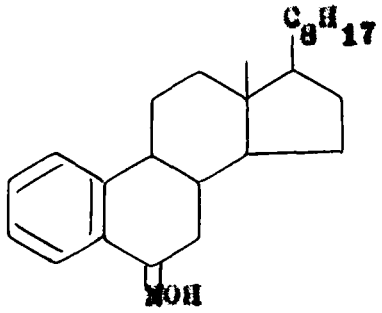
Expulsion of acetylene from the fragment ion m/e 146(s) may well occur for the formation of the ion m/e 120. Its composition (C_7H_6NO) supports, in part, this assumption (Scheme 29).

Scheme - 29



Oximation of the ketone (CLXIII): 19-Norcholesta-1,3,5(10)-trien-6-one oxime (CLXXXVI)

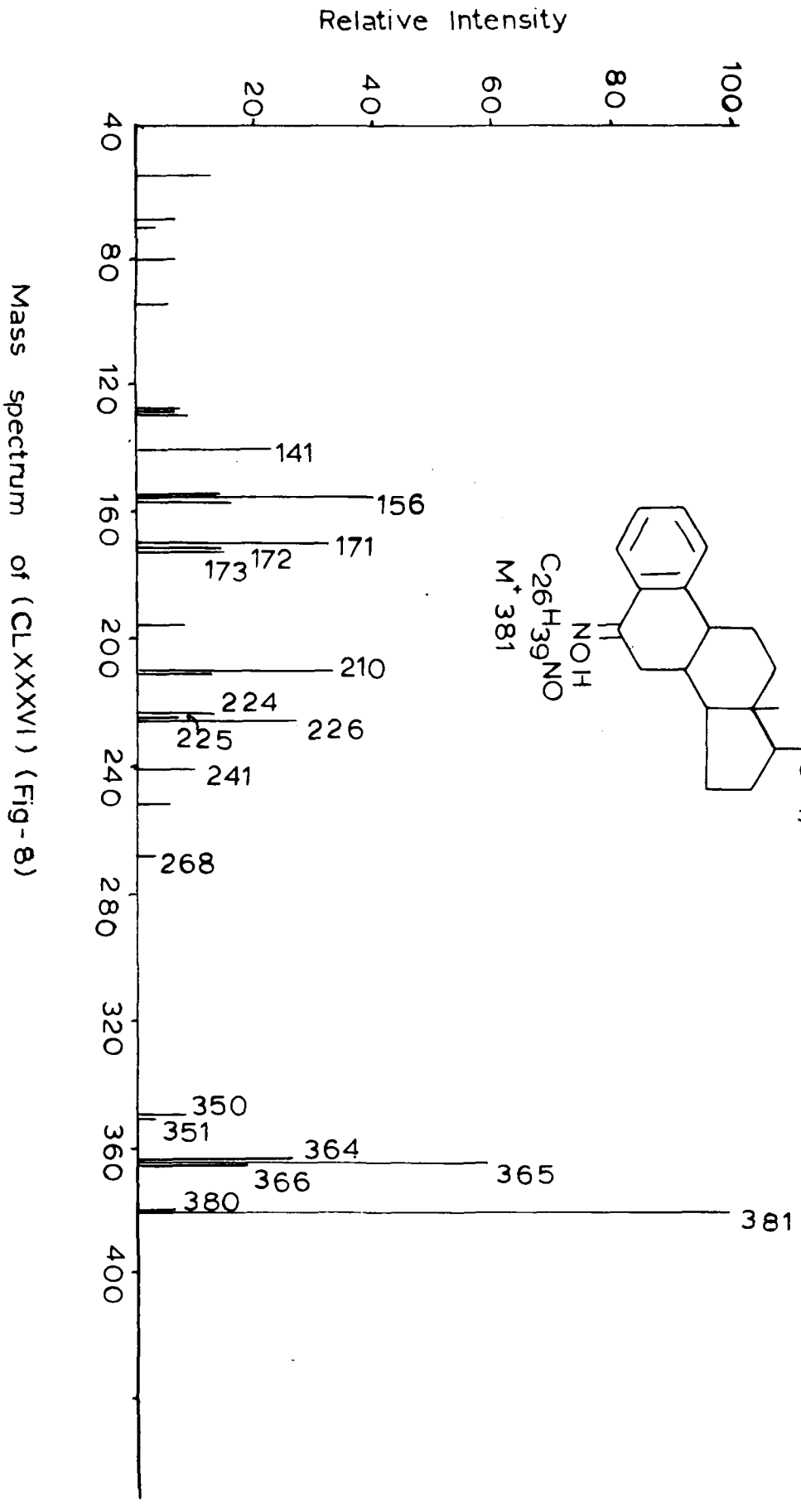
The oxime (CLXXXVI) was prepared from the ketone (CLXIII) according to usual method. The oxime (CLXXXVI) m.p. 195° analysed correctly for $C_{26}H_{39}NO$ and its i.r. spectrum gave bands at 3250s (N-OH), 3070 (C=C-H), 1620, 1600 cm^{-1} (C=C, aromatic). The n.m.r. spectrum of the oxime (CLXXXVI) gave signals at δ 8.2br (1H, disappeared on addition of D_2O; =N-OH), 7.5br,s (4H, C1-H, C2-H, C3-H, and C4-H, aromatic protons), 0.73s (C13-CH_3), 0.86 and 1.0 (other methyl protons). The oxime (CLXXXVI) was shown to be homogeneous by t.l.c. in different solvent system and by repeated crystallisation.



(CLXXXVI)

(Fig.8)

The mass spectrum of 19-norcholesta-1,3,5(10)-trien-6-one oxime (CLXXXVI) gave molecular ion peak at m/e 381 ($C_{26}H_{39}NO$) (base peak) followed by other significant peaks at m/e 380, 366, 365, 364, 363, 351, 350, 349, 296, 268, 241, 226, 224, 210, 173, 172, 171, 156, 141 and lower mass peaks.

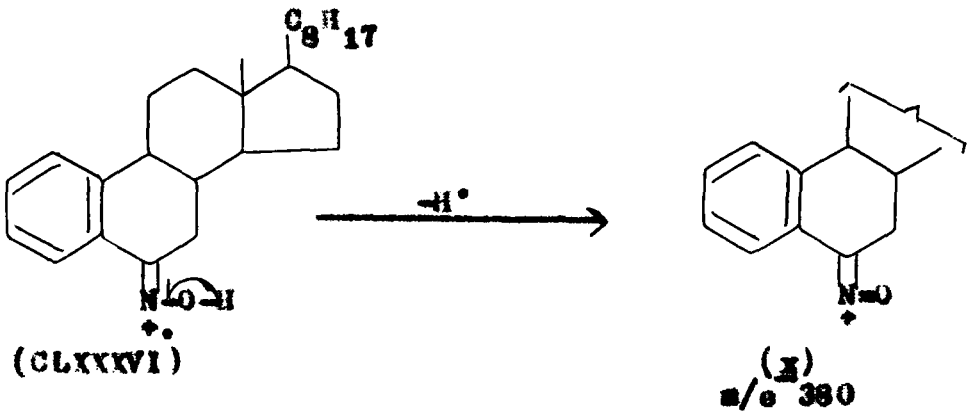


Mass spectrum of (CLXXXVI) (Fig-8)

The formation of the more significant ions can be rationalized according to Schemes given below. The mechanistic schemes suggested are tentative in the absence of mass spectra of appropriate deuterated analogues. However, it is gratifying to note strong similarity between the mass spectrum of (CLXXXVI) with that of 5α-cholestan-6-one oxime (CLXXXVIII)[179].

m/e 380 (M-H)

Obviously, this fragment ion (X) is obtained by the loss of hydrogen from the molecular ion, probably following the way shown below.



m/e 366

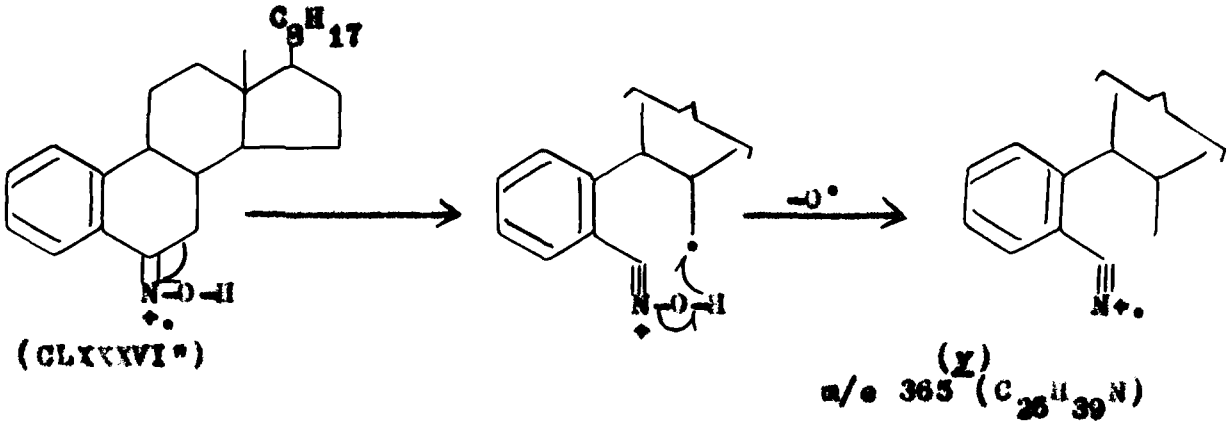
This fragment ion may arise by the loss of one of the methyl groups from the molecular ion. However, this ion also

represents the molecular ion ($M^{\cdot+}$ 366) of the parent ketone(CLXIII). However, accurate mass measurement of this showed this to be a nitrogen bearing species with the composition ($C_{26}H_{39}NO$) thus eliminating the possibility of the presence of the parent ketone as an impurity. This precaution was considered necessary to avoid any confusion arising out of the presence of (CLXIII). The ion m/e 366, most probably arises by the ejection of the angular methyl group.

m/e 365 and 364

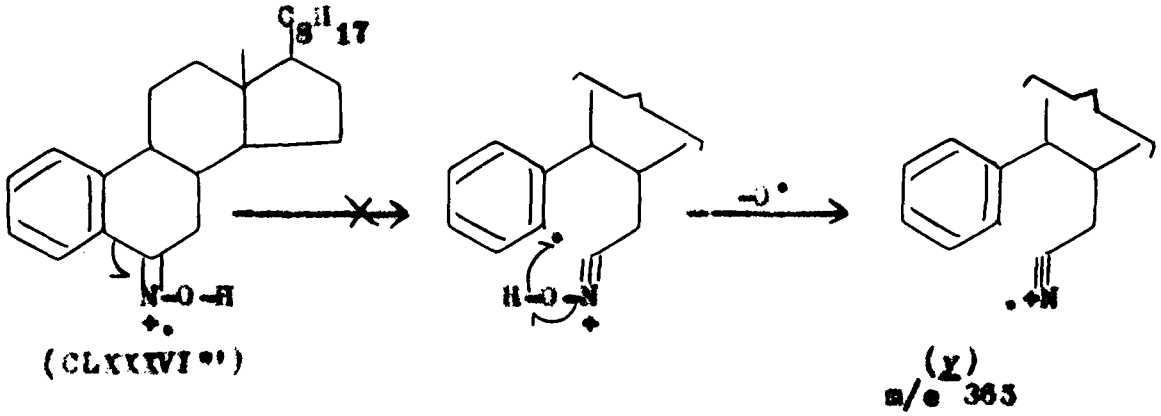
The fragment ion m/e 365(y) is due to the loss of the oxygen from the oximino moiety as is established by accurate mass measurement ($C_{26}H_{39}N$). The loss of an oxygen from oxime is a well established phenomenon which can be shown to occur according to Scheme 30.

Scheme - 30



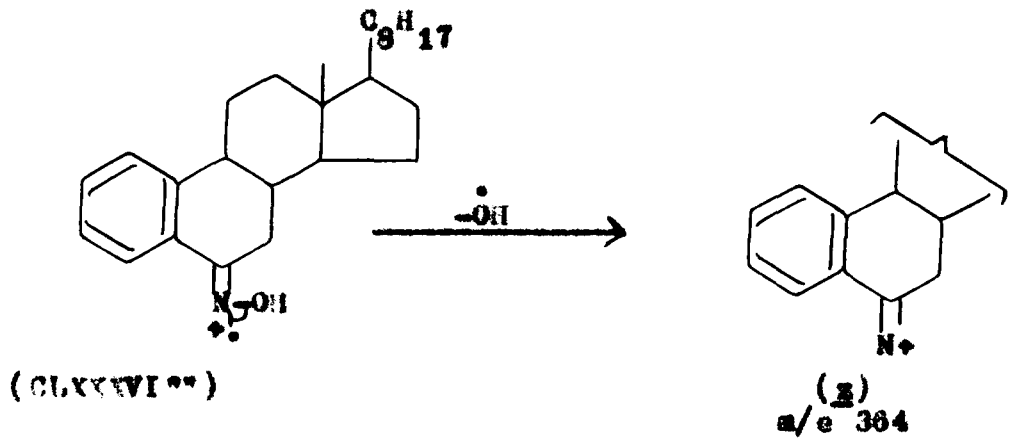
The alternative path for the loss of oxygen (Scheme 31) is not being considered because this will involve the cleavage of a vinylic bond.

Scheme - 31



Similarly, the fragment ion m/e 364 (z) arises as a result of the loss of OH from the molecular ion.

Scheme - 32



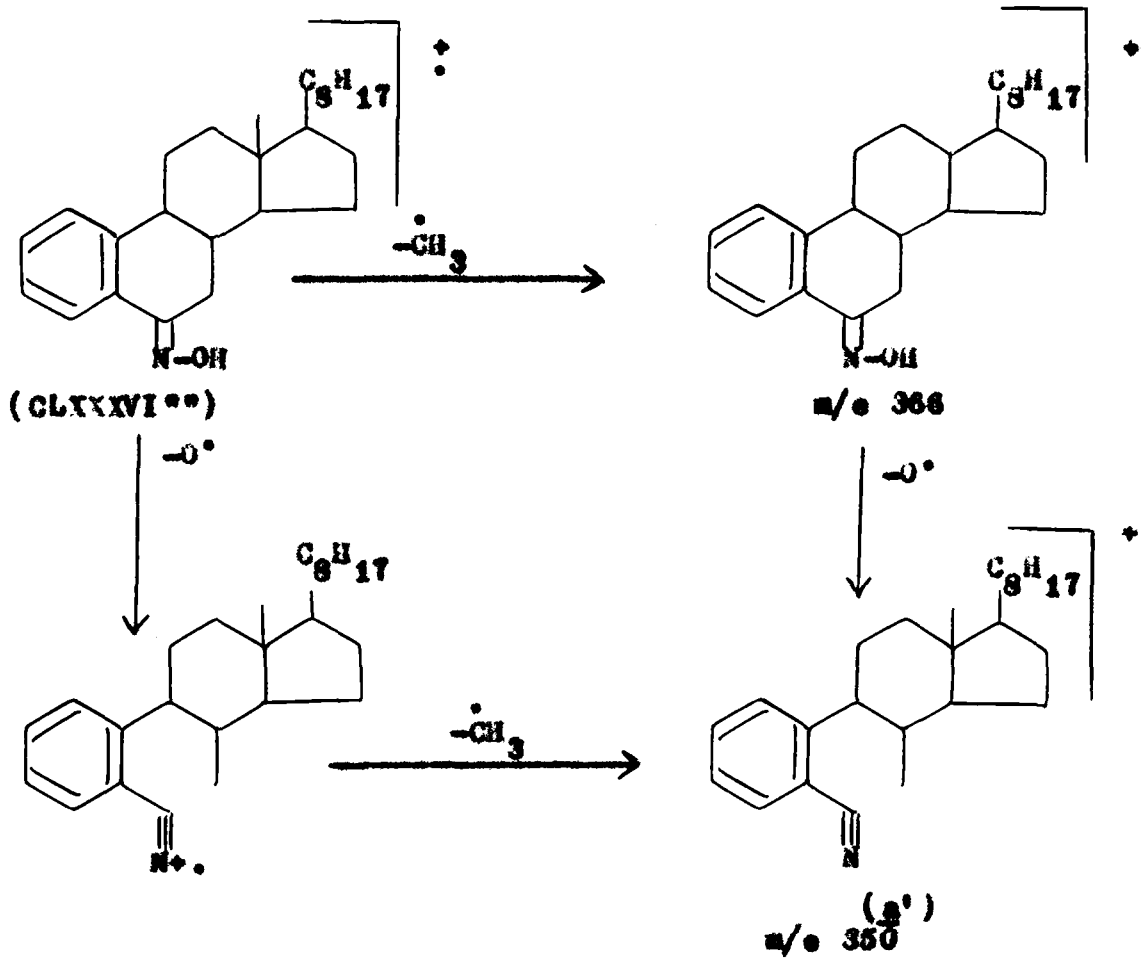
m/e 363

This fragment ion corresponds to the loss of water molecule from the molecular ion. The loss of water molecule from oximes is of common occurrence[167].

m/e 350

The fragment ion peak at m/e 350 (g') can arise either from the ion m/e 366 by the loss of oxygen or from the ion m/e 365 (y) by the loss of a methyl group or by both the process.

Scheme - 33



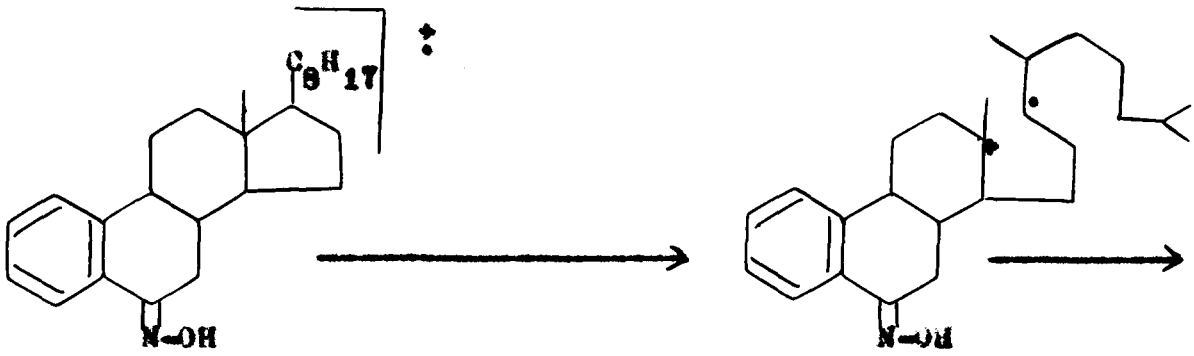
m/e 368

This fragment ion is best explained by the expulsion of the side chain (C_8H_{17}, mass unit 113) from the molecular ion (m/e 381).

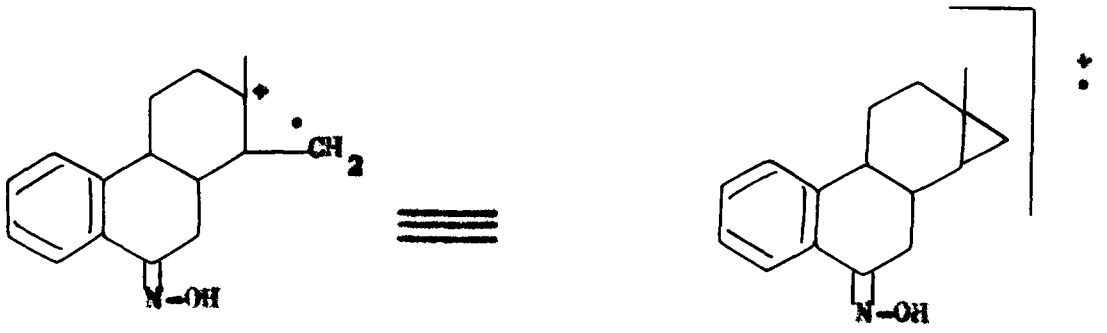
m/e 241

This fragment ion (b') can be shown to arise by the loss of the side chain and part of ring D from the molecular ion (Scheme 34).

Scheme - 34



(CLXXXVI ***)

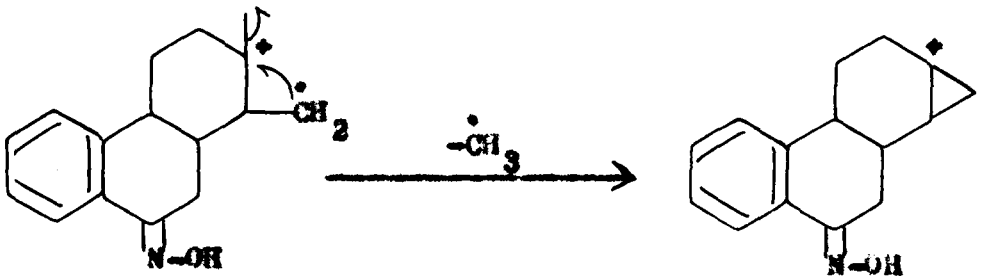


(b')
m/e 241

m/e 226

This fragment ion may be shown to arise by the loss of a methyl group from the ion m/e 241 (b') Scheme 35.

Scheme - 35



(b')
m/e 241

(c')
m/e 226

m/e 224

This fragment ion obviously results by the loss of hydroxyl group from the ion m/e 241 (b').

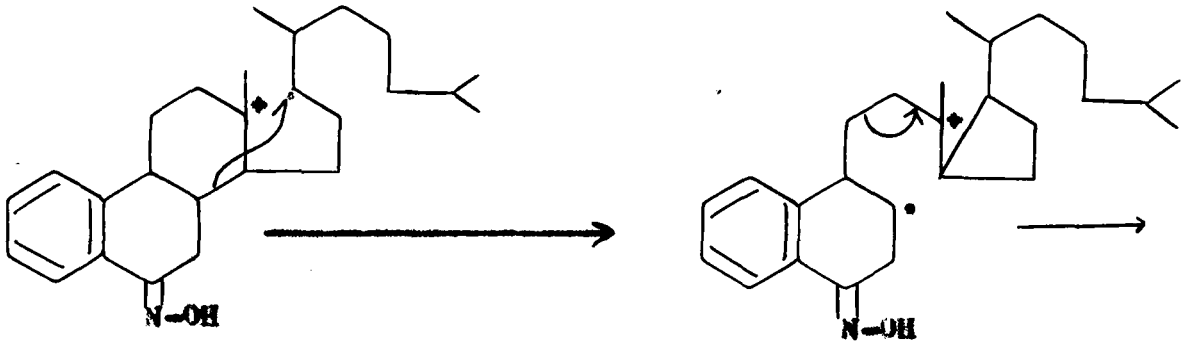
m/e 210

The formation of ion m/e 210 may occur by the loss of oxygen from the ion m/e 226 (c').

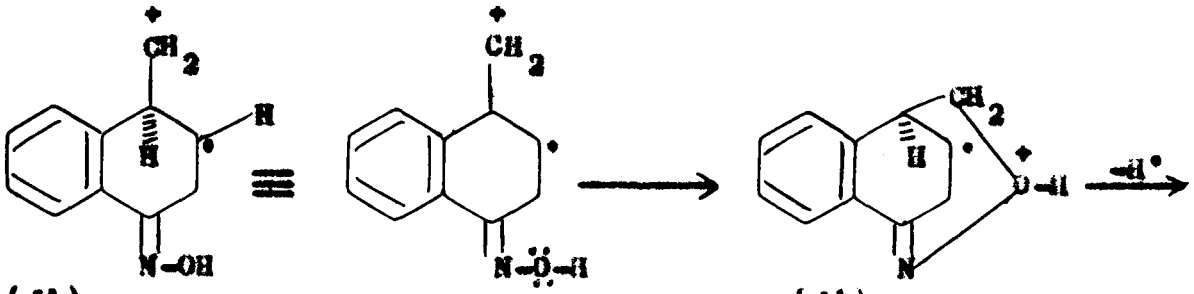
m/e 173, 172, 171 and 141

These fragment ions can be rationalized rather by a more "imaginative" pathways as shown in Scheme 36.

Scheme - 36

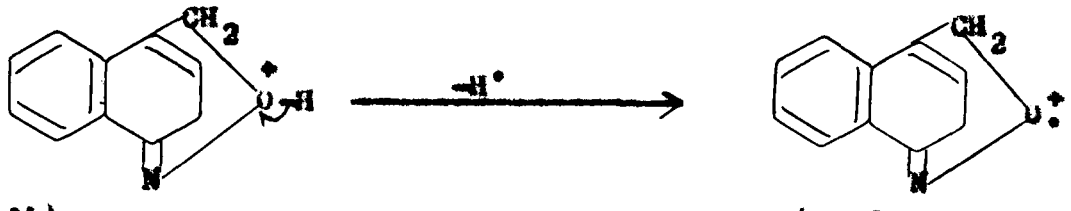


(CLXXXVI[m+·])



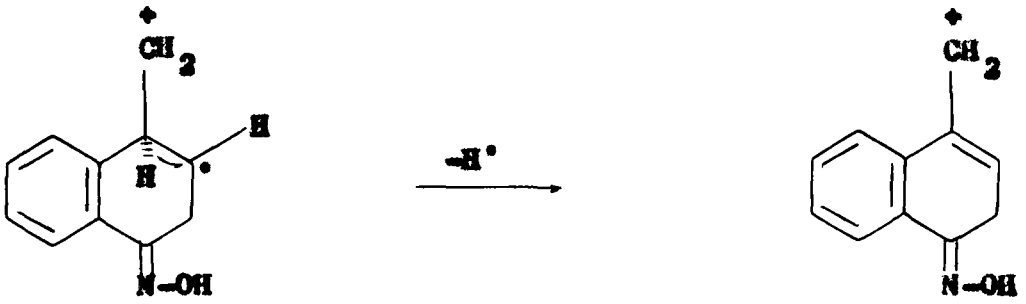
(d')
m/e 173 ($C_{11}H_{11}NO$)

(d')
m/e 173



(d')
m/e 172

m/e 171

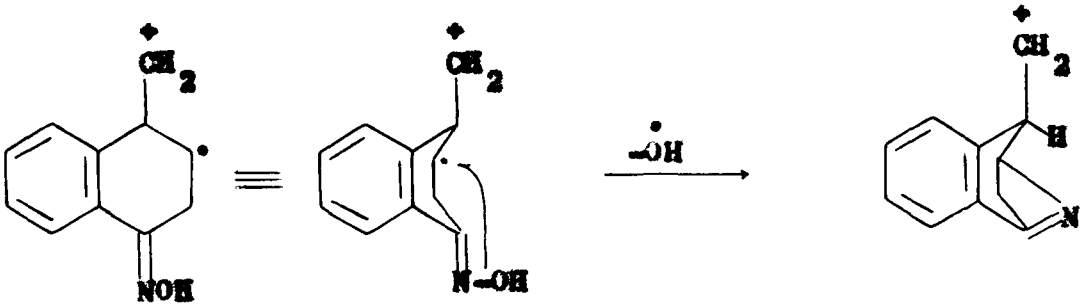


(d')
m/e 173

m/e 172

m/e 156

The fragment ion m/e 156 (e') can be obtained by the loss of OH from the ion m/e 173 (d').



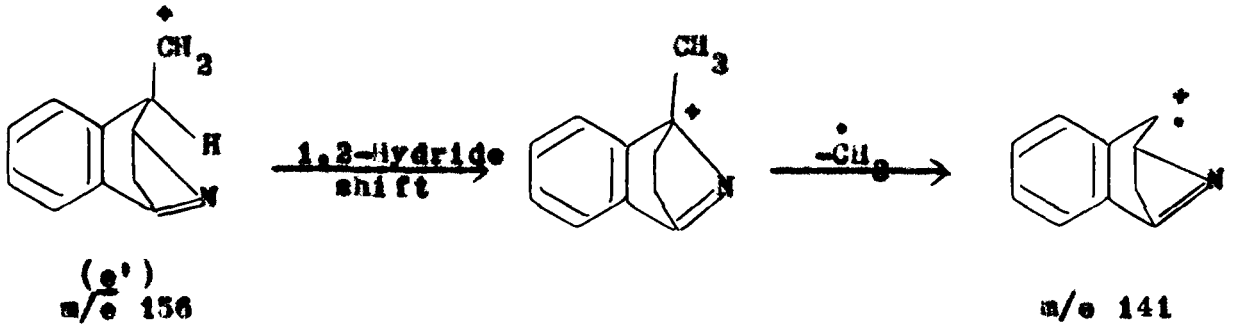
(d')
m/e 173

(e')
m/e 156

m/e 141

The formation of the fragment ion m/e 141 from the ion m/e 156 (e') is shown to occur according to Scheme 37.

Scheme - 37

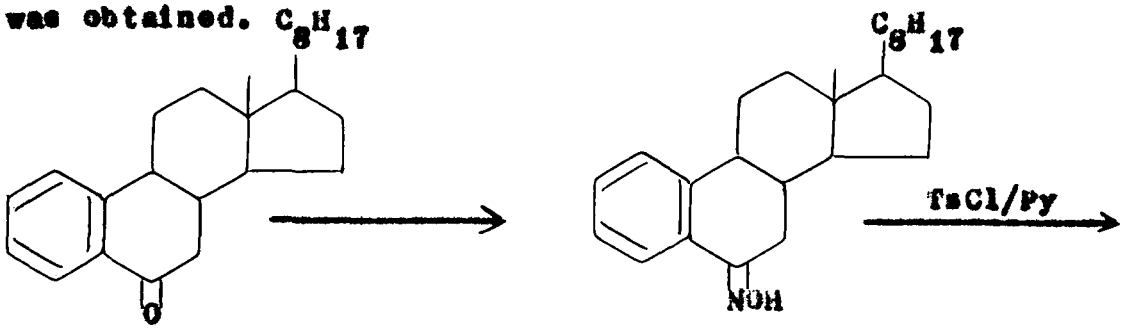


(e') m/e 156

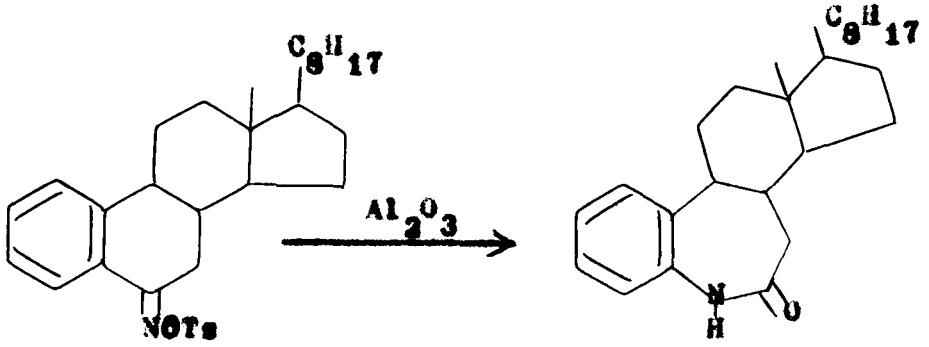
m/e 141

Beckmann rearrangement of the oxime (CLXXXVI)

The oxime (CLXXXVI) was treated with p-toluenesulphonyl chloride in pyridine and after usual work up of the reaction mixture, the corresponding oxime tosylate (CLXXXVII), m.p. 170° was obtained.



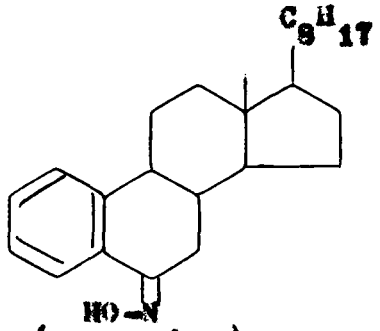
(CLXIII) (CLXXXVI)



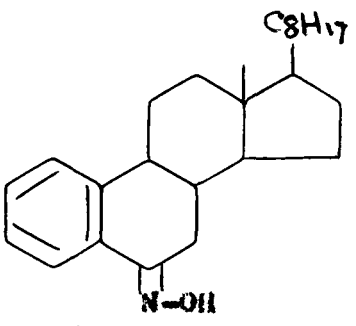
(CLXXXVII) (CLXXXIV)

The i.r. spectrum of the oxime tosylate (CLXXXVII) gave band at about 1600 cm^{-1} (C=C, aromatic). Its n.m.r. spectrum gave two doublets at δ 8.15 and 7.5 integrating for 4 protons (typical of p-disubstituted benzene with J value of 9 Hz). A partly overlaping singlet for 4 protons was observed at δ 7.48 which is ascribable to protons of ring A of the steroid. Other signals were observed at δ 2.55s (3H, $\underline{CH}_3$ group attached to benzene ring of the tosylate part), 2.2m (2H, C7-$\underline{H}_2$), 0.71s (3H, C13-$\underline{CH}_3$), 0.98 and 0.96 (other methyl protons). The oxime tosylate (CLXXXVII) without further purification was subjected to column chromatography over alumina column. This also provided a single lactam (CLXXXIV) m.p. and m.m.p. 88°.

The formation of a single lactam (CLXXXIV) from the oxime (CLXXXVI) shows that the oximino hydroxyl group is away from ring A i.e. it is an anti-oxime (CLXXXVI-b); the syn oxime (CLXXXVI-a) would have resulted in the formation of the isomeric lactam (CLXXXV).



(syn-oxime)
(CLXXXVI-a)

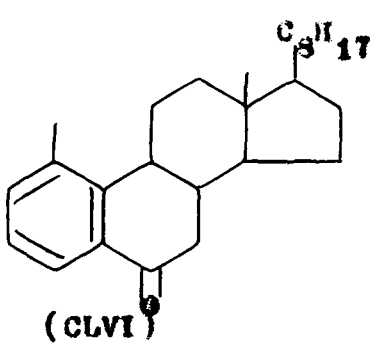


(anti-oxime)
(CLXXXVI-b)

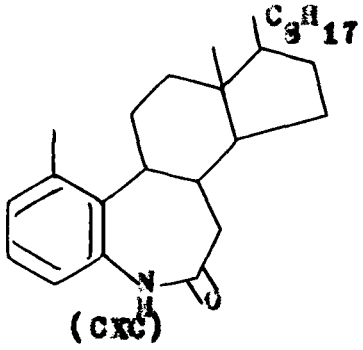
Schmidt reaction of 1-methyl-19-norcholesta-1,3,5(10)-trien-6-one (CLVI); 1-Methyl-19-nor-6-aza-6-homocholesta-1,3,5(10)-trien-7-one (CXC)

The ketone (CLVI) was subjected to Schmidt reaction in two ways; one using sodium azide and polyphosphoric acid and the other employed, sodium azide sulphuric acid in benzene. However, as in the case of (CLXIII), the former method failed in this case also.

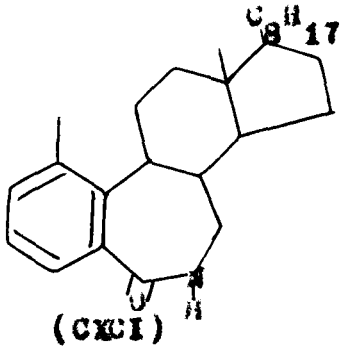
The reaction of the ketone (CLVI) with sodium azide and sulphuric acid in benzene afforded a single lactam (CXC), m.p. 171°, which analysed for $C_{27}H_{41}NO$. Its i.r. spectrum gave band at 3190, 3130(NH), 3030 (C=C-H), 1670 (CONH), 1645 and 1595 cm^{-1} (C=C, aromatic). The u.v. spectrum showed absorption maxima at 240 nm. However, these spectral values are indecisive in arriving at correct formulation of the lactam, since two possibilities existed for its representation; (CXC) and (CXCI).



(CLVI)



(CXC)



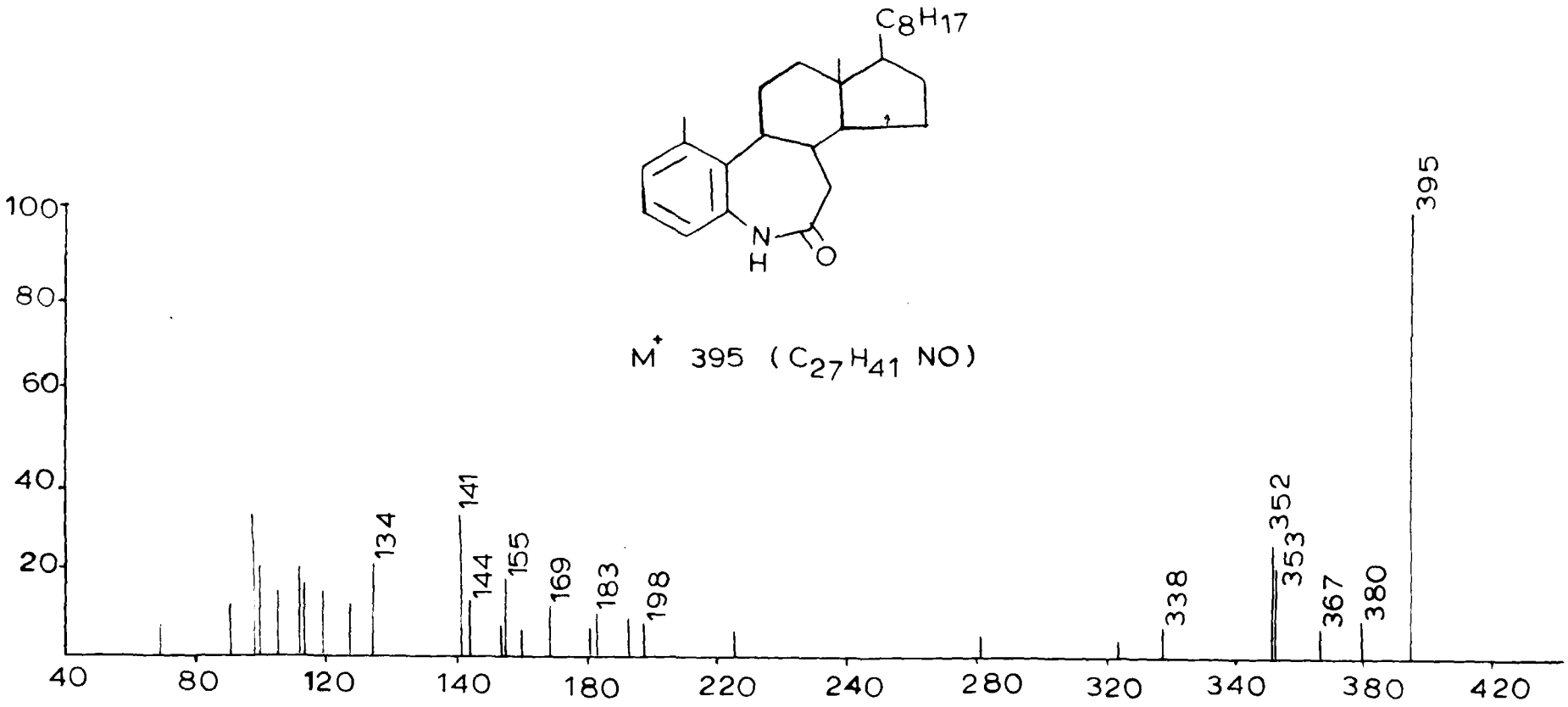
(CXCI)

The n.m.r. spectrum of the compound, m.p. 171° helped in achieving a distinction between (CXC) and (CXCI). The spectrum gave signals at δ 10.15s (1H, disappeared on addition of D_2O, CONH; no other part of the spectrum was affected after deuterium exchange); 6.95m (3H, C2-H, C3-H, C4-H; vinylic protons of ring A), 2.45s (3H, CH_3-attached to benzenoid ring A; C1-CH_3), 2.2m (2H, C7-H_2), 0.91, 0.85, 0.8 (other methyl protons). By advancing the same arguments as was done in the case of the lactam (CLXXXIV), one can safely conclude that the n.m.r. spectrum supports the structure (CXC) in an unambiguous term.

The mass spectrum of 1-methyl-19-nor-6-aza-8-homocholesta-1,3,5(10)-trien-7-one (CXC)(Fig. 9) gave molecular ion peak at m/e 395 ($C_{27}H_{41}NO$) alongwith other important peaks at m/e 380 (M-CH_3), 367(M-CO), m/e 353, m/e 352, m/e 338, m/e 332, m/e 198, m/e 183, 169, m/e 155, m/e 144, m/e 141, and lower mass peaks. As expected there are certain points of resemblances between the spectra of (CLXXXIV) and (CXC). However, there are also some points of difference between the two spectra which could be attributed to the presence of methyl group at C1 in (CXC). The formation of some of the important fragment ions peak in the spectrum of (CXC) has been rationalised according to schemes given below.

<u>m/e 380</u>

This fragment ion can arise by the loss of one of the methyl groups from the molecular ion.



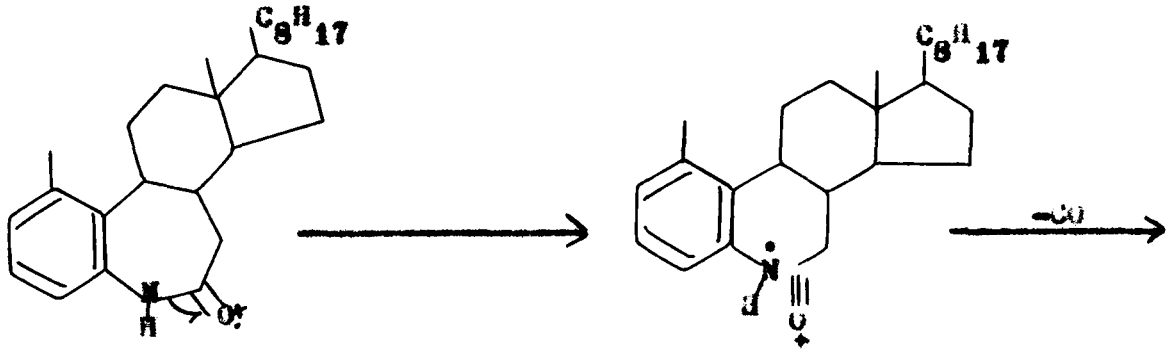
Mass spectrum of (CXC) (Fig 9)

m/e 367

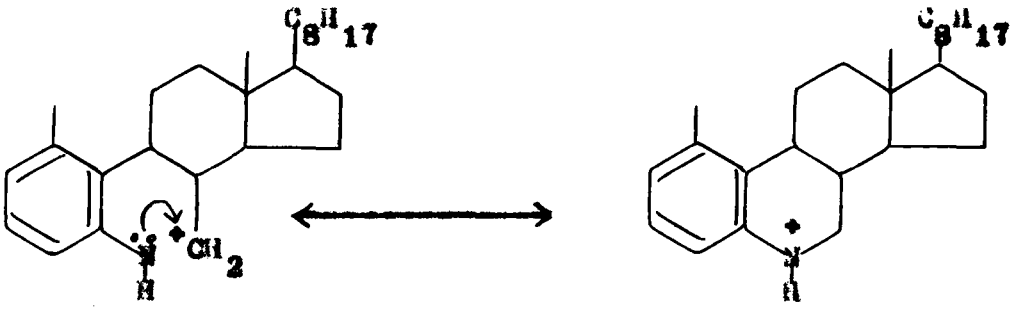
The loss of CO from the molecular ion can account for the formation of this fragment ion (f'). However, there are two possible modes of cleavage giving rise to this ion.

Scheme - 38

A.

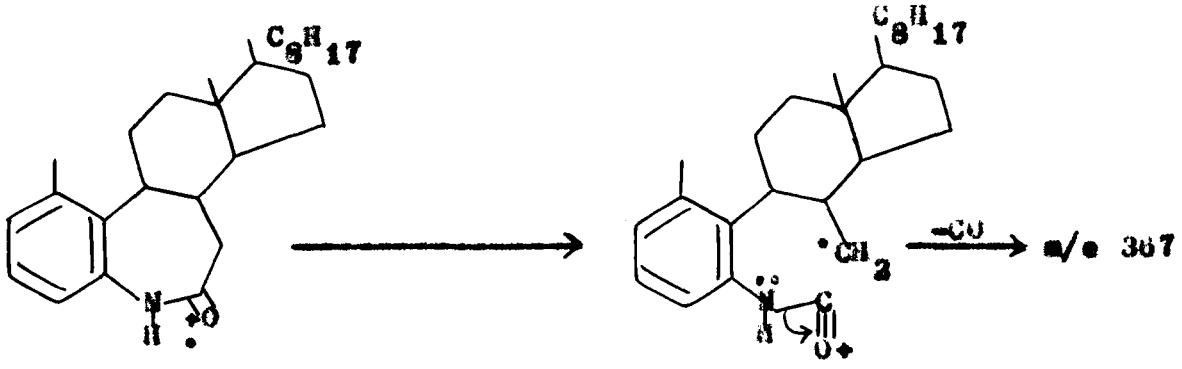


(CXC')



(f')
m/e 367

B.

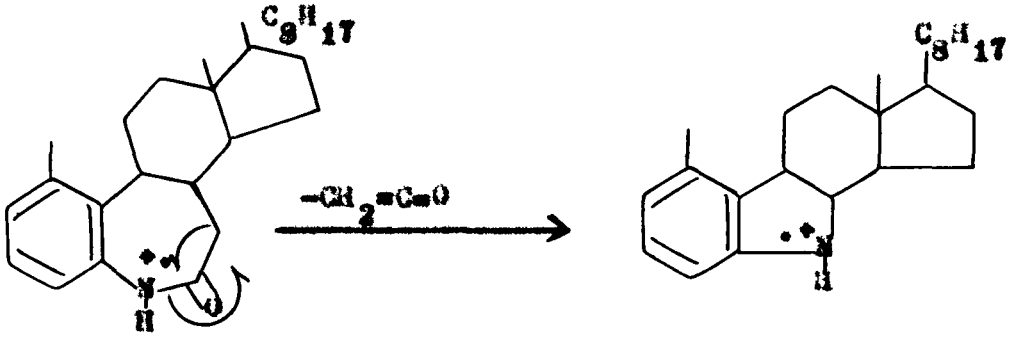


(CXC")

m/e 353

This ion is compatible with the loss of a ketene molecule from the molecular ion. This assumption finds support by accurate mass measurement of this ion, which showed the composition ($C_{25}H_{39}N$). It should be pointed out that the loss of ketene, in the case of (CLXXXIV) did not occur from the molecular ion but only at a later stage (Scheme 23).

Scheme - 39

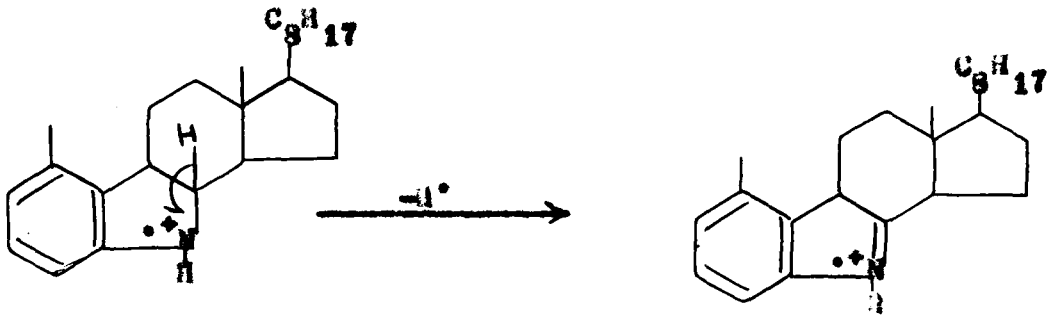


(CXC^a) (f') m/e 353 ($C_{25}H_{39}N$)

m/e 352 (M-43)

Obviously there are two ways to account for the genesis of this fragment ion. One could be the loss of hydrogen from the ion m/e 353 (f') and the other could involve successive losses of CO and CH_3 group from the molecular ion. Both the possibilities are important. In the following scheme, the loss of hydrogen from the ion m/e 353 (f') has been shown.

Scheme - 40



(f')
m/e 353

m/e 352

m/e 338

This fragment ion can be obtained by the loss of a methyl group from the ion m/e 353 (f').

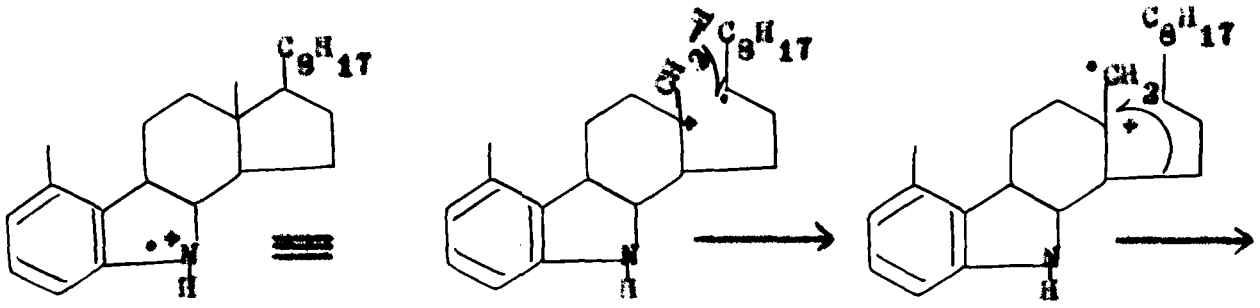
m/e 282

This fragment ion obviously results by the loss of the side chain (C_8H_{17}, mass unit 113) from the molecular ion.

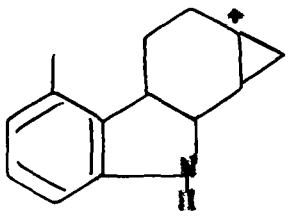
m/e 198

The fragment ion m/e 198 (g') can be shown to be derived from the ion m/e 353 (f') by the loss of the side chain and ring D. This assumption finds support from the composition of this ion ($C_{14}H_{16}N$). The genesis of the ion m/e 198 (g') can be shown according to Scheme 40-a.

Scheme - 40-a



(g')
m/e 353

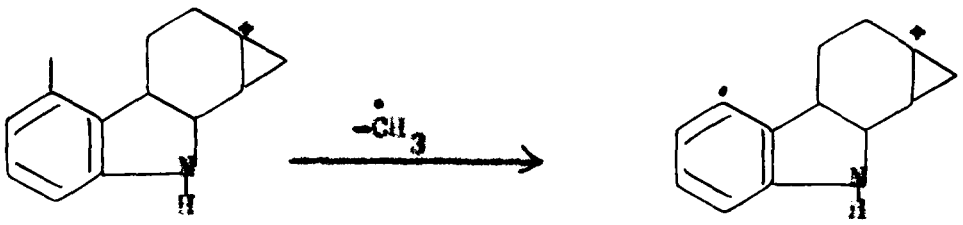


(g')
m/e 198 ($C_{14}H_{16}N$)

m/e 183

This fragment ion obviously results by the loss of a methyl group from the fragment ion m/e 198 (g') (Scheme 41).

Scheme - 41



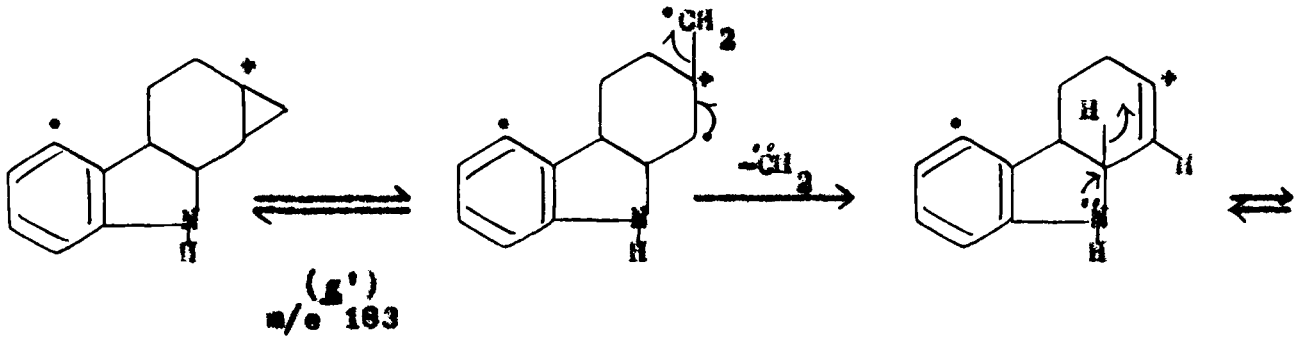
(g')
m/e 198

(h')
m/e 183

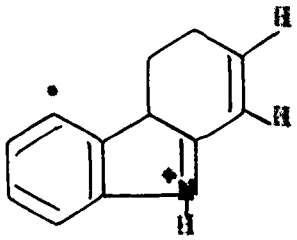
m/e 169

This fragment ion ($C_{12}H_{11}N$) can be shown to arise by the loss of a methylene group from the ion m/e 183 (g'). Several possible structures compatible with the composition ($C_{12}H_{11}N$) can be suggested as given in Scheme 42.

Scheme - 42

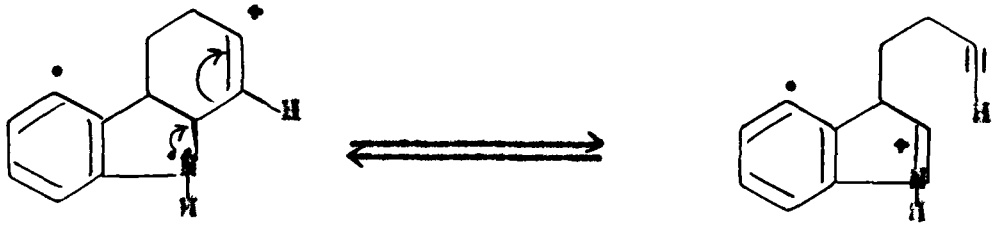


(g')
m/e 183



(1')
m/e 169 ($C_{12}H_{11}N$)

and/or



m/e 169 ($C_{12}H_{11}N$)

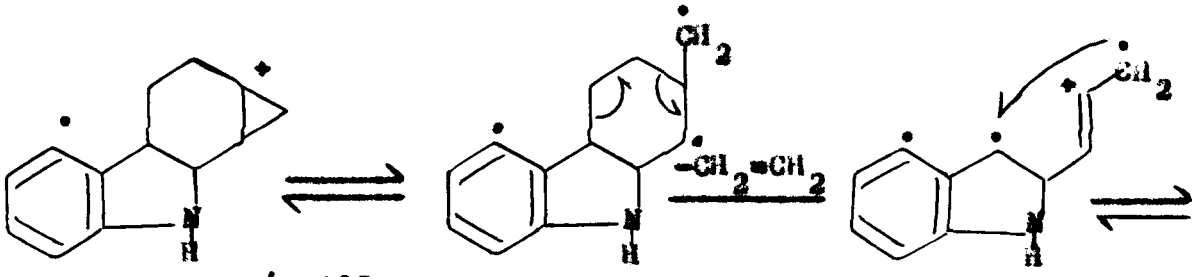
m/e 155

The composition of this fragment ion ($C_{11}H_9N$) suggests that this species can generate from the ion m/e 169 (1') by the loss of a methylene group or by the loss of ethylene from the ion m/e 183 (g'). The latter possibility seems to be more attractive for the reason of being simpler than the former suggestions. However, both the possibilities have been considered in Scheme 43.

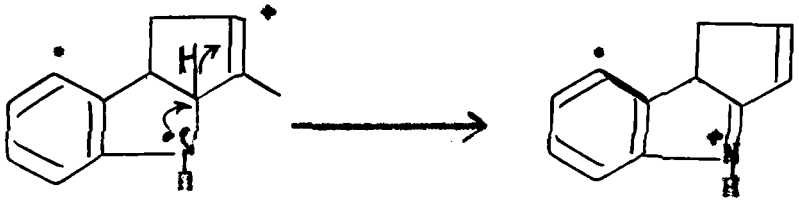
Scheme - 43

From m/e 183

A.

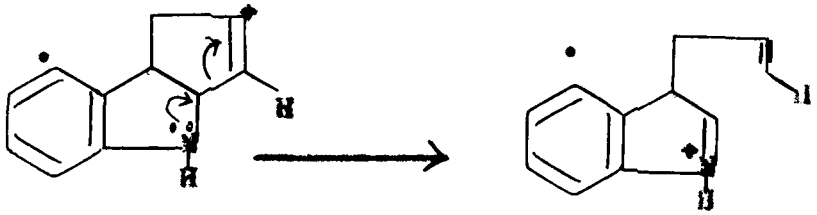


m/e 183



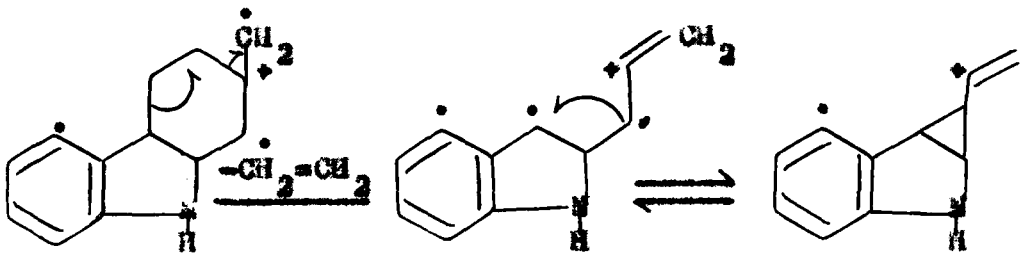
(1)
m/e 155 ($C_{11}H_9N$)

or



(1')
m/e 155

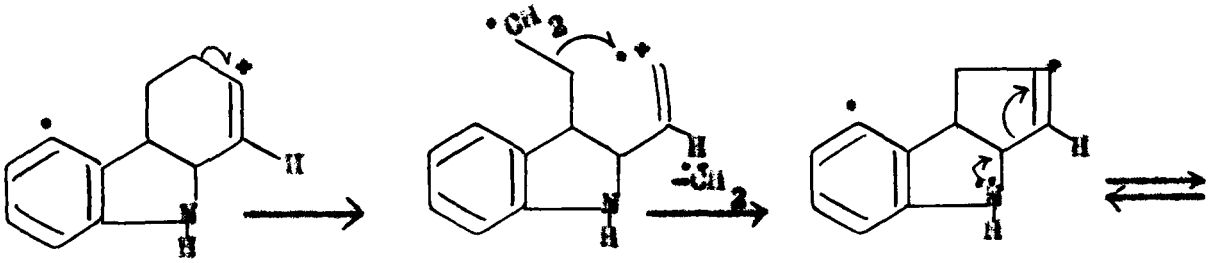
B.



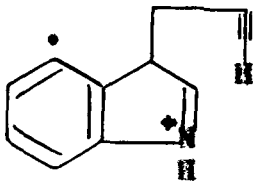
m/e 155

(g')
m/e 183

From m/e 169



(1')
m/e 169



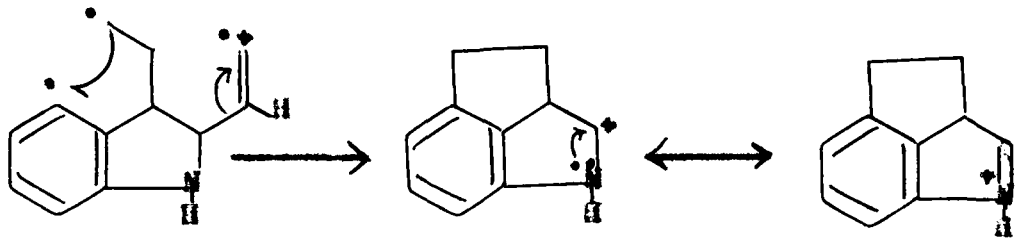
(1')
m/e 155

m/e 144

The composition of this fragment ion ($C_{10}H_{10}N$) suggests that this ion can be obtained from the ion m/e 169 by the loss

of mass unit 25. Such a loss from the ion m/e 169 has been rationalised according to Scheme 44.

Scheme - 44



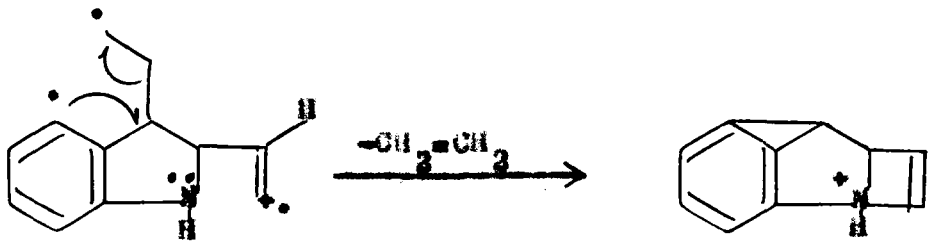
(1')
m/e 169

m/e 144 ($C_{10}H_{10}N$)

m/e 141

This fragment ion can be shown to arise from the ion m/e 169 by the loss of ethylene molecule. This assumption is in agreement with the composition of the ion m/e 141 ($C_{10}H_7N$). The Scheme 45 outlines the proposal, m/e 169 —— m/e 141.

Scheme - 45

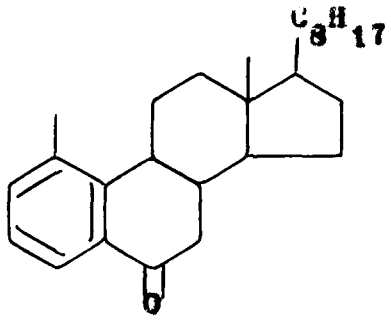


(1')
m/e 169

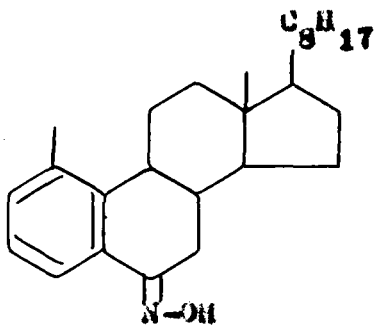
m/e 141 ($C_{10}H_7N$)

Oximation of the ketone (CLVI); 1-methyl-19-norcholeste-1,3,5(10)-trien-6-one oxime (CLXXXIX)

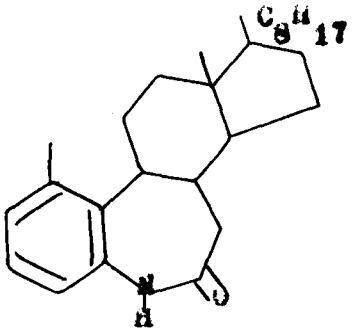
The ketone (CLVI) with hydroxylamine hydrochloride and sodium acetate in refluxing ethanol afforded the corresponding oxime (CLXXXIX), m.p. 185° which analysed for $C_{27}H_{41}NO$. Its homogeneity was checked by repeated crystallisations and by t.l.c. in different solvent systems. Its i.r. spectrum showed bands at 3250s (N-OH), 3070w (C=C-H), and 1600 cm^{-1} (C=C, aromatic)[155] The n.m.r. spectrum gave signals at δ 9.45br,s (1H, disappeared on addition of D_2O; N-OH), 7.85m (1H, C3-H), 7.16s (2H, C2-H and C4-H) 2.15s (3H, C1-CH_3), 0.69s (C13-CH_3), 0.83 and 0.93 (other methyl signals).



(CLVI)



(CLXXXIX)



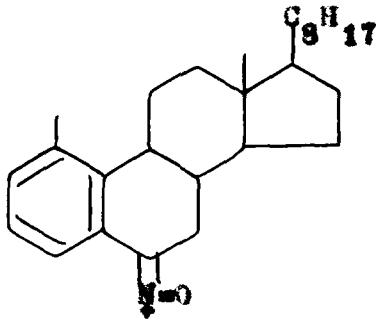
(CXC)

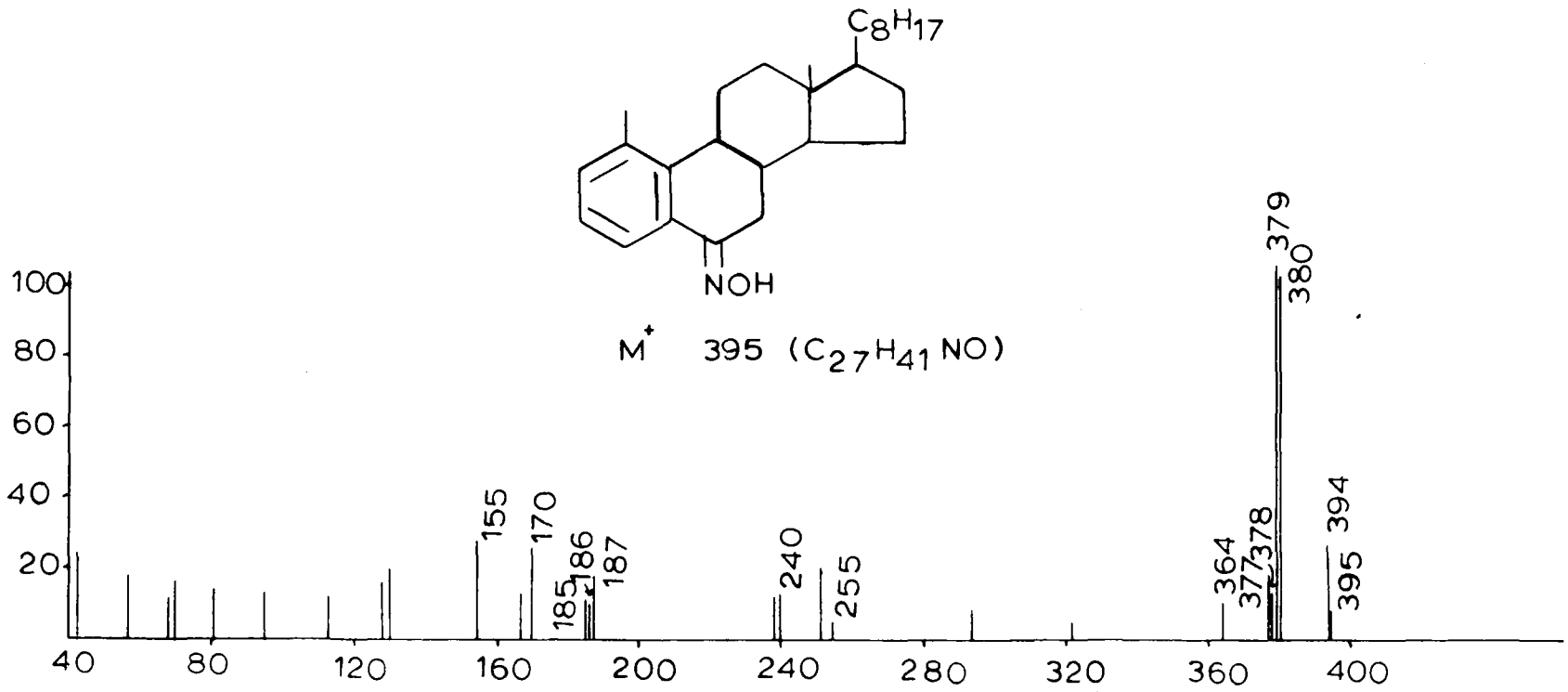
The Beckmann Rearrangement of the oxime (CLXXXIX)

The Beckmann rearrangement of the oxime (CLXXXIX) by p-toluenesulphonyl chloride in pyridine, followed by chromatography over alumina gave a single lactum (CXC), m.p. and m.m.p. 170-171°.

The mass spectrum of 1-methyl-19-nor-cholesta-1,3,5(10)-trien-6-one oxime (CLXXXIX)(fig. 10) gave molecular ion peak at m/e 395 ($C_{27}H_{41}NO$) along with other prominent peaks at m/e 394, 380, 379, 378, 377, 365, 364, 362, 310, 282, 255, 240, 238, 224, 187, 186, 185, 170, 155, and lower mass peaks. The mass spectrum of the oxime (CLXXXIX) is comparable with the one (CLXXXVI) previously discussed. However, some important fragment ions are given in the table 3 and these can be explained on the basis of similarity of fragmentation pattern observed between the oxime (CLXXXIX) and 19-norcholesta-1,3,5(10)-trien-6-one oxime(CLXXXVI). Therefore, the formation of the individual fragment ions is not being repeated here. The fragment ions m/e 394, 380, 379, 378, 377 and 255 result by the loss of a hydrogen, methyl group, oxygen, hydroxyl group, water molecule and side chain with part of ring D, respectively, from the molecular ion (m/e 395).

Table - 3

Fragments	m/e	Composition
	394	$C_{27}H_{40}NO$



Mass spectrum of (CLXXXIX) (Fig 10)

Table - 3(Contd.)

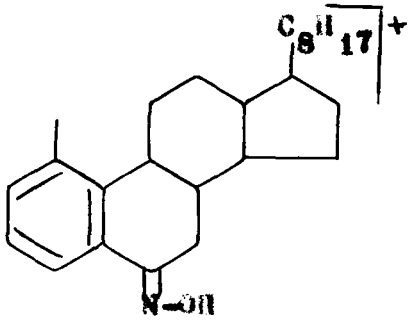
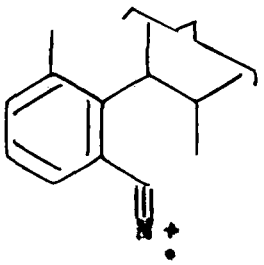
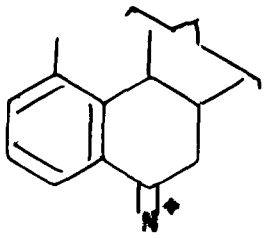
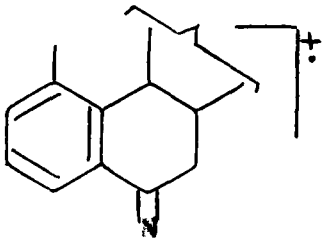
Fragments	m/e	Composition
	380	$C_{28}H_{38}NO$
	379	$C_{27}H_{41}N$
	378	$C_{27}H_{40}N$
	377	$C_{27}H_{39}N$

Table - 3(Contd.)

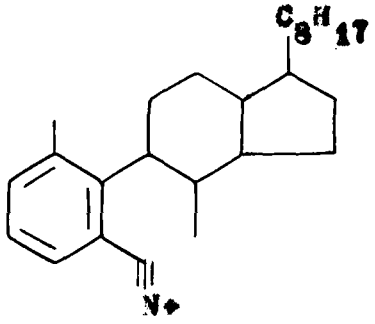
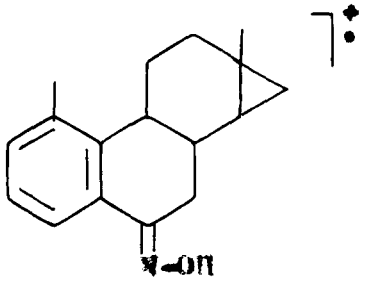
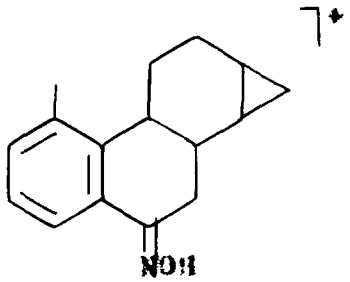
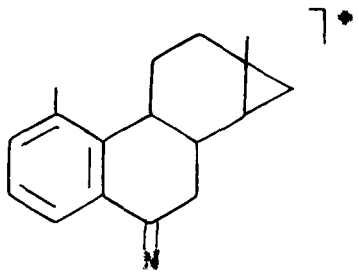
Fragments	m/e	Composition
	364	$C_{26}H_{39}N$
	255	$C_{17}H_{21}NO$
	240	$C_{16}H_{18}NO$
	238	$C_{17}H_{20}N$

Table - 3(Contd.)

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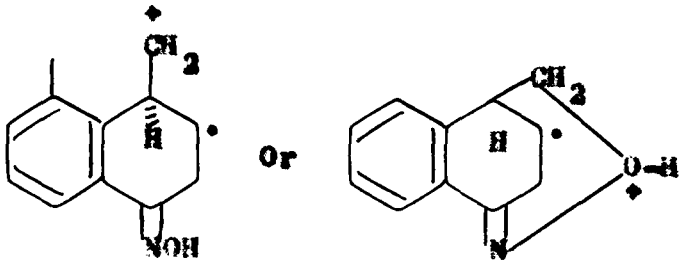
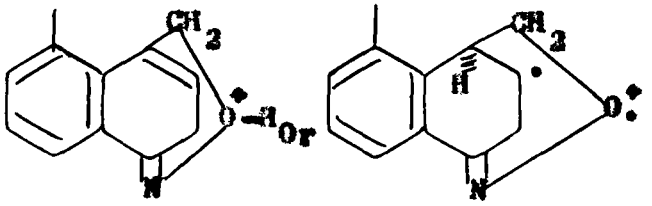
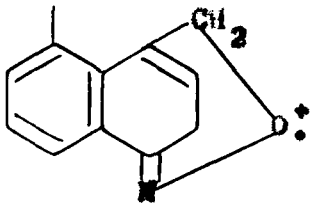
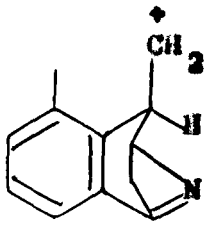
	187	$C_{12}H_{13}NO$
	186	$C_{12}H_{12}NO$
	185	$C_{12}H_{11}NO$
	170	$C_{12}H_{12}N$

Table - 3(Contd.)

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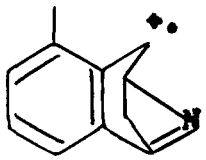	155	$C_{11}H_9N$

EXPERIMENTAL

All melting points are uncorrected. Infrared spectra were determined in KBr with a Perkin-Elmer 237 Spectrophotometer. N.m.r. spectra were run in $CDCl_3$ on a Varian A60/HA 100 instrument with TMS as the internal standard. Ultraviolet spectra were determined in 95% ethanol with an Unicam Sp 800 spectrophotometer. Thin-layer chromatographic plates were prepared from silica gel G and sprayed with perchloric acid (20% aqueous solution). Light petroleum refers to a fraction of b.p. 60-80°. N.m.r. values are given in ppm (s, singlet; d, doublet, t, triplet; br, broad; umc, unresolved multiplet centered at; mc, multiplet centered at). I.r. values are given in cm^{-1} (s, strong; m, medium; w, weak; br, broad).

PART - I

3β-Chlorocholest-5-ene

Freshly purified thionyl chloride (75 ml) was added gradually to cholesterol (100 g) at room temperature. A vigorous reaction ensued with the evolution of gaseous products; when the reaction slackened the mixture was gently heated at a temperature

of 50-60° on a water bath for 1 hour, and then poured into crushed ice with stirring. The yellow solid thus obtained was filtered under suction and washed several times with ice-cooled water and air dried. Recrystallization from acetone gave 3β-chlorocholest-5-ene (95.5 g), m.p. 95-96° (reported[130] m.p. 96-97°). It gave positive Beilstein test and a yellow colour with tetranitromethane in chloroform.

3β-Chloro-6-nitrocholest-5-ene

To a well stirred mixture of 3β-chlorocholest-5-ene (12 g), glacial acetic acid (80 ml) and nitric acid (25 ml; d, 1.52) at temperature below 20°, was added sodium nitrite (3.0 g) gradually over a period of 2 hours. After the complete addition of sodium nitrite, the mixture was further stirred for about 1 hour, ice-cooled water (200 ml) was added and the yellowish solid thus separated, was filtered and air dried. The desired product was recrystallized from ethanol as needles (8.3 g), m.p. 151-52° (reported[190] m.p. 153°).

3β-Chloro-5α-cholestan-6-one (CLVIII)

A solution of 3β-chloro-6-nitrocholest-5-ene (12 g) and acetic acid glacial (240 ml) was heated just to get a clear solution. To this was added water (24 ml) at regular intervals

and allowed to come down to room temperature and then zinc dust (24 g) was added gradually in small portions with constant shaking. The suspension was heated under reflux for 4 hours. The hot solution was poured into ice-cooled water. The organic matter was extracted with ether and the ethereal solution was washed with water, sodium bicarbonate solution (5 %) and water and dried over anhydrous sodium sulphate. Evaporation of the solvent furnished (CLVIII) as an oil which was crystallized from methanol (8.7 g), m.p. 128-29° (reported[134] m.p. 129°).

3β-Chloro-5α-bromocholestan-6-one (CLIX)

3β-Chloro-5α-cholestan-6-one (CLVIII) (4.3 g) in ether (50 ml) at 0°C was treated with a solution of bromine in glacial acetic acid (40 ml; 5 %); the addition of bromine solution was completed over a period of 1 hour. The reaction was catalysed with a few drops of hydrobromic acid. Decolourisation proceeded rapidly and the crystalline material separated after the addition of approximately half of the bromine solution. The reaction mixture was further allowed to stand at 0°C for half an hour, to ensure complete crystallization. The solid was filtered under suction and recrystallized from light petroleum from which 3β-chloro-5α-bromocholestan-6-one (CLIX)(3.5 g) separated as white crystals, m.p. 124-26° (homogeneous by t.l.c., solvent system pet.ether-ether); ν max 1712 (C=O), 765 (C-Cl), 640 (C-Br);

δ 4.3s (C3-$\underline{H}$, α-oriented, axial), 2.4d (J = 7 Hz, C7-$\underline{H}_2$), δ 1.0s (C10-$\underline{CH}_3$), 0.69s (C13-$\underline{CH}_3$), 0.75 and 0.90s (other methyl signals).

Analysis. Found: C, 65.6; H, 9.3.

$C_{27}H_{44}OCl$ requires : C, 64.8; H, 8.8 %.

3β-Chloro-5,7β-dibromo-5α-cholestan-6-one (CLXI)

To a solution of 3β-chloro-5α-cholestan-6-one (CLVIII) (4.0 g) in ether (30 ml) at room temperature was added a solution of bromine in acetic acid (40 ml; 5 %); the addition of bromine solution was completed over a period of half an hour. The reaction mixture (catalysed by a few drops of hydrobromic acid) was allowed to stand at room temperature for 3 days. The solid material thus obtained was filtered under suction and air dried. Recrystallization from pet.ether-ether afforded the haloketone (CLXI) (3.6 g) m.p. 174-75° (homogeneous by t.l.c., solvent system pet. ether-ether); ν max 1725 (C=O), 768 (C-Cl), 736 and 635 cm^{-1} (C-Br); δ 5.35d (C7-$\underline{H}$, α-oriented, axial, J = 9 Hz), 4.39br (C3-$\underline{H}$, α-oriented, axial), 1.1s (C10-$\underline{CH}_3$), 0.72s (C13-$\underline{CH}_3$), 0.93 and 0.94 (other methyl signals).

Analysis. Found: C, 55.35; H, 7.45

$C_{27}H_{43}OClBr_2$ requires: C, 55.93; H, 7.59 %.

Dehydrohalogenation of 3β-chloro-5α-bromocholestan-6-one (CLIX)

The bromoketone (CLIX)(10.0 g) in freshly distilled pyridine (70 ml) was heated under reflux for 10 hours. The colour of the reaction mixture became dark red during the course of the reaction. Most of the solvent was removed by distillation under reduced pressure; the residue diluted with water and extracted with ether and the ethereal solution was washed successively with water, dilute hydrochloric acid, water, sodium bicarbonate solution (5%) and water and dried over anhydrous sodium sulphate. Removal of the solvent gave a semi solid material (5.0 g) which was chromatographed over silica gel (100 g). Fractions of 10 ml were collected. Elutes from pet.ether-benzene (20:1) gave cholestn-2,4-dien-6-one (CLXV) which was crystallized from pet. ether-ether (1.0 g), m.p. 127-28° (reported[150] m.p. 129-30°); M^+ 382 ($C_{27}H_{42}O$); λ max 314 nm (ϵ7621); ν max 1670s (-C=C-C=C-C=O), 1623 cm^{-1} (-C=C-); δ 6.53 mc (C2-H), 6.13 dist.d (C3-H and C4-H), 2.3 mc (C7-H_2), 1.0 (C10-CH_3), 0.7 (C13-CH_3), 0.95 and 0.85 (other methyl signals).

Elution with pet.ether-benzene (15:1) afforded 5α-cholestan-3,6-dione (CLVII)(1.0 g), m.p. 168° (reported[151] m.p. 169°); M^+ 400 ($C_{27}H_{44}O_2$); ν max 1710 (C=O); δ 2.1-2.7 (7 protons, C2-H_2, C4-H_2, C5-H, C7-H_2), 0.9 (C10-CH_3), 0.7 (C13-CH_3), 0.85 and 0.90 (other methyl signals).

Further elution with pet.ether-benzene (12:1) gave 3α-5-cyclo-5α-cholest-7-en-6-one (CLXII) which was crystallized from pet.ether (0.9), m.p. 118-19°; λ max 232 nm; ν max 1695 (C=C-C=O), 1030, 1010 cm^{-1} (cyclopropan)[163], 1605 cm^{-1} (-C=C-); δ 6.22 (C8-H, vinylic proton), 2.55 (C9-H and C14-H, allylic protons), 1.22 ($C10-CH_3$), 0.76 ($C13-CH_3$), 0.94 and 0.88 (other methyl signals).

Analysis. Found: C, 84.6; H, 10.7

$C_{27}H_{42}O$ requires: C, 84.8; H, 10.9%.

Elution with pet.ether-benzene (9:1) gave 19-norcholesta-1,3,5(10)-trien-6-one (CLXIII) which was crystallized from pet.ether (2.0 g), m.p. 110° (reported[166] m.p. 110°); M^+ 366 ($C_{26}H_{38}O$); λ max 233 nm together with another band at 295 nm (aromatic ring system); ν max 1690 (C=C-C=O), 3060 (C=C), 1600 cm^{-1} (aromatic system); δ 8.05m (C4-H, J = 8 Hz, o-coupled; J = 2 Hz, m-coupled), 7.3m (3H, C1-H, C2-H and C3-H), 2.35m (3H, $C7-H_2$, and C9-H, allylic to 9(10)-double bond).

Analysis. Found: C, 85.03; H, 10.5

$C_{26}H_{38}O$ requires: C, 85.24; H, 10.38%.

3β,5,6β-Trihydroxy-5α-cholestane

A mixture of cholesterol (20 g) and formic acid (20 ml; 99%) was heated on a water bath at 70-80° for 5 minutes and then allowed to attain room temperature. Hydrogen peroxide (20 ml;

30 %) was added to the mixture and it was kept at room temperature for 12 hours with occasional shaking. Boiling water (ca 300 ml) was added with stirring and the reaction mixture allowed to attain room temperature when a white granular solid separated which was filtered under suction and air dried. The solid was dissolved in methanol (300 ml) and the solution heated with sodium hydroxide solution (20 ml; 25 %) for 10 minutes on a steam bath. It was acidified with hydrochloric acid and diluted with boiling water (300 ml). The triol obtained on cooling was collected by filtration under reduced pressure and recrystallized from methanol (18 g), m.p. 237-39° (reported[191] m.p. 237-39°).

3β,5-Dihydroxy-5α-cholestan-6-one

To a solution of 3β,5,6β-trihydroxy-5α-cholestane (10 g) in dioxan (90 ml) was added N-bromosuccinimide (4.5 g) at about 25°. After 15 minutes at 25°, the reaction mixture was cooled in an ice bath and the product was collected by filtration under suction and washed thoroughly with 50 % methanol (6.5 g), m.p. 231-33° (reported[191] m.p. 231-33°).

The mother liquor was diluted with water and extracted with ether; the ethereal solution washed with water and dried over anhydrous sodium sulphate. It provided an additional quantity of the diolone (2.3 g), m.p. 231-33°.

3β,5-Dihydroxy-5α-cholestan-6-one-3-tosylate

The diolone (2.5 g) was dissolved in pyridine (10 ml; distilled over solid KOH) and to the resultant solution was added p-toluenesulphonyl chloride (1.3 g). The reaction mixture was allowed to stand at room temperature for 12 hours and then diluted with water. The precipitate thus obtained was filtered under suction and air dried. The crude product was subjected to column chromatography (Al_2O_3). Elute from benzene-ether mixture (4:1) provided the tosylate (1.2 g), recrystallized from acetone-hexane mixture, m.p. 130-132° (reported[159] m.p. 161-63°).

5-Hydroxy-5α-cholest-2-en-6-one

A solution of 3β,5-Dihydroxy-5α-cholestan-6-one-3-tosylate (1.0 g) in pyridine (50 ml, distilled over solid KOH) was heated under reflux for 36 hours. The pyridine was removed by distillation under reduced pressure and the residue extracted with ether. The ethereal solution was washed with hydrochloric acid, water, sodium bicarbonate solution (5%) and water and dried over anhydrous sodium sulphate. Removal of the desiccant and the solvent provided a semi solid material (ca 1 g) which was subjected to column chromatography (Al_2O_3; 20 g). Elutes from hexane-benzene mixture gave the desired product, recrystallized from light pet.ether (0.3 g), m.p. 140° (reported[182] m.p. 140-41°), ν max 3500m (OH), 1720s cm^{-1} (C=O).

Cholest-2,4-dien-6-one (CXXV)

A solution of cholest-2-en-5α-ol-6-one(1.7 g) in absolute methanol (75 ml) and conc. sulphuric acid (2.6 ml) was heated under reflux for 2 hours. The reaction mixture after cooling was poured into water and extracted with ether. The ethereal solution was washed with water, sodium bicarbonate solution (5 %), and water and dried over anhydrous sodium sulphate. Removal of the desiccant and the solvent provided a semi solid which was subjected to column chromatography (Al_2O_3). Elutes from pet. ether-benzene (4:1) provided the desired compound (CXXV), which was recrystallized from pet.ether (0.53 g), m.p. 127-29° (reported[159] m.p. 129-30°).

Dehydrohalogenation of 3β-chloro-5,7β-dibromo-5α-cholestan-6-one (CLXI)

The haloketone (CLXI)(5.0 g) in freshly distilled pyridine (40 ml) over KOH was heated under reflux for 10 hours. The colour of the reaction mixture became dark red during the course of the reaction. Most of the solvent was removed by distillation under reduced pressure, the residue diluted with water and extracted with ether and the ethereal solution was washed successively with water, dilute hydrochloric acid, water, sodium bicarbonate solution (5 %) and water and dried over anhydrous sodium sulphate. Removal of the solvent provided a brown coloured

semi solid material (4.0 g) which was chromatographed over silica gel (90 g). Fraction of 10 ml were collected. Elutes from pet. ether-benzene (6:1) gave 1-methyl-19-norcholesta-1,3,5(10)-trien-6-one (CLVI) which was crystallized from pet.ether (1.1 g), m.p. 140°; M^+ 390 ($C_{27}H_{40}O$); λ max 255 nm together with another band at 300 nm (aromatic system); ν max 1685 (C=C-C=C-C=O), 1600 cm^{-1} (-C=C-, aromatic); δ 7.95d,d (1H, J = 8 Hz, o-coupled and J = 2Hz, m-coupled; C4-H), 7.35 (2H, C2-H and C3-H), 2.41s ($C1-CH_3$), 0.73 ($C13-CH_3$), 0.91 and 0.82 (other methyl signals).

Analysis. Found: C, 85.06; H, 11.12

$C_{27}H_{40}O$ requires: C, 85.26; H, 10.52%.

PART I - II

3β-Chlorocholest-5-en-7-one (CLXXIX)

During 1 hour a solution of chromium trioxide (36 g) in 30% aqueous acetic acid (36 ml) was added to a vigorously stirred solution of cholesteryl chloride (30 g) in acetic acid (600 ml) at 55°C. After 2 hour the excess of chromium trioxide was destroyed by ethanol. The solution was distilled under reduced pressure to one-third of its volume and water (15 ml) added. The crystalline chloroketone (CLXXIX)(8.0 g) deposited from the cold solution, m.p. 144° (reported[171] m.p. 144-145°); M^+ 413/420 ($C_{27}H_{43}OCl$); λ max 343 nm; ν max 1675 (-C=C-C=O), 1635 cm^{-1} (C=C-C=O), 3030w (C=C-H) and 768 cm^{-1} (C-Cl); δ 5.35s (1H, C6-H, vinylic proton), 3.96br (1H, $W_{\frac{1}{2}}$ 20 Hz, α-oriented, axial, C3-H), 1.25s (3H, C10-CH_3), 0.70 (C13-CH_3), 0.83 and 0.93 (other methyl protons).

Analysis. Found: C, 77.58; H, 10.36

$C_{27}H_{43}OCl$ requires : C, 77.32; H, 10.26 %.

Oximation of the ketone (CLXXIX): 3β-Chlorocholest-5-en-7-one oxime (CLXXX)

A mixture of the ketone (CLXXIX)(1.75 g) hydroxylamine hydrochloride (4.5 g), crystalline sodium acetate trihydrate

(7.0 g) and methanol (90 ml) was heated under reflux for 2 hours on a water bath. Excess of the solvent was removed under reduced pressure and the residue poured into ice-cooled water. The crude oxime thus obtained was filtered, air-dried and recrystallized from pet.ether-ether (1.21 g), m.p. 197° (positive Beilstein test); νmax (3294s (≡N-H), 1643 cm^{-1} (-C=N), 1620 cm^{-1} (-C=C-); δ 7.89br (1H, disappeared on addition of D_2O; ≡N-H), 6.76s (1H, C6-H, vinylic proton), 3.55br (1H, $W_{\frac{1}{2}}$ 22 Hz, α-oriented, C3-H, axial), 3.9s dist.d (2H, C4-H_2), 1.15s (3H, C10-CH_3), 0.71s (3H, C13-CH_3), 1.0, 0.91 and 0.83 (other methyl protons).

Analysis. Found: C, 74.75; H, 9.98; N, 3.46

$C_{27}H_{44}NOCl$ requires : C, 74.65; H, 10.11; N, 3.45.

Beckmann rearrangement of the oxime (CLXXX); 3β-Chloro-7a-aza-8-homocholest-5-en-7-one (CLXXXI)

(1) 3β-Chlorocholest-5-en-7-one oxime (CLXXX)(1 g) was added as quickly as possible with stirring to thionyl chloride (10 ml; freshly purified) at 0° and solution was immediately poured into 4N potassium hydroxide solution kept on water bath at 30°. The solid thus obtained was filtered, washed with water and air-dried. Recrystallization from acetone gave the lactam (CLXXXI)(0.43 g), m.p. 170-71° (positive Beilstein test); M^+ 433/435 ($C_{27}H_{44}NOCl$); νmax 3290, 3240, 3180 (-NH), 1665 (C=C-C-NH), 1624 cm^{-1} (C=C); δ 6.35br (1H, disappeared on addition of D_2O; CO-NH), 5.95s (1H,

C6-H, vinylic proton), 3.9br (1H, $W_{\frac{1}{2}}$ 22 Hz, C3-H, α-oriented, axial), 3.3m (1H, C3-H), 2.8m (2H, C4-H), 1.48s (3H, C10-CH_3), 0.70s (C13-CH_3), 0.93 and 0.85 (other methyl protons).

Analysis. Found: C, 74.73; H, 9.75; N, 3.45

$C_{27}H_{44}NOCl$ requires: C, 74.73; H, 9.75; N, 3.45

(ii) The oxime (CLXXX)(0.6 g) dissolved in pyridine (6 ml; freshly distilled over KOH) and p-toluenesulphonyl chloride (0.6 g) was added to the solution and the reaction mixture was kept at room temperature for 15 hrs. It was poured into ice-cooled water, extracted with ether, washed with water, dilute hydrochloric acid, sodium bicarbonate solution (5%) and finally with water and dried (anhydrous sodium sulphate). Removal of the solvent gave an oil (0.33 g) which was kept over a column of neutral alumina (25 g; each fraction of 15 ml was taken) for about 1 hour and then eluted. Elution with light pet.ether-ether (4:1) gave the chlorolactam (CLXXXI) as an oil which was crystallised from pet.ether-ether (100 mg), m.p. and m.m.p. 170-71°; (positive Beilstein test)(t.l.c. and i.r. identical with the lactam (CLXXXI) prepared using $SOCl_2$).

Schmidt reaction of the ketone (CLXXIX): 3β-chloro-7a-aza-B-homocholest-5-en-7-one (CLXXXI)

A mixture of the ketone (CLXXIX)(1.0 g) and polyphosphoric acid (60 g; freshly prepared) was heated to a temperature of

50-60° on a water bath and sodium azide (170 mg) was added in portions with stirring. The reaction mixture was kept at this temperature for 9 hours and then it was poured into ice-cooled water and extracted with ether. The ethereal layer was washed with water, sodium bicarbonate solution (5%) and water and dried (anhydrous sodium sulphate). Removal of the solvent gave an oil (500 mg), which was chromatographed over silica gel (20 g; each fraction of 15 ml was taken). Elution with pet.ether-ether (1:1) gave the lactam (CLXXXI), recrystallized from pet.ether-ether (250 mg), m.p. and m.m.p. 170-71°; (positive Beilstein test) (t.l.c. and i.r. identical with the lactam (CLXXXI) obtained using Beckmann rearrangement conditions.

Oximation of the ketone (CLXIII): 19-norcholesta-1,3,5(10)-trien-6-one oxime (CLXXXVI)

19-Norcholesta-1,3,5(10)-trien-6-one (CLXIII)(0.4 g), hydroxylamine hydrochloride (0.7 g), sodium acetate trihydrate (0.9 g) and ethanol (50 ml) were mixed together and the mixture was heated under reflux for 1 hour. The excess of the solvent was removed under reduced pressure and the residue was diluted with cold water. The solid oxime (CLXXXVI) thus obtained was recrystallized from pet.ether-ether (300 mg), m.p. 191-95°; M^+ 391 ($C_{26}H_{39}NO$); λ max 255 nm; ν max 3230s (N-H), 3070 (C=C-H), 1620, 1600 cm^{-1} (C=C, aromatic); δ 8.2br (1H, disappeared on addition of D_2O; N-OH), 7.5brs (4H, C1-H, C2-H, C3-H and C4-H, aromatic

protons), 0.73s ($C13-CH_3$), 0.96 and 1.0 (other methyl protons).

Analysis. Found: C, 81.21; H, 10.2; N, 4.30

$C_{26}H_{39}NO$ requires : C, 81.97; H, 10.21; N, 3.95%.

Beckmann rearrangement of the oxime (CLXXXVI); 6-aza-B-homo-19-norcholesta-1,3,5(10)-trien-7-one (CLXXXIV)

The oxime (CLXXXVI)(300 mg) was dissolved in pyridine (25 ml; freshly distilled over KOH) and p-toluenesulphonyl chloride (500 mg) was added to the solution and the reaction mixture was kept at room temperature for 15 hours. It was poured into ice-cooled water, extracted with ether, washed with water, dilute hydrochloric acid, sodium bicarbonate solution (5%) and finally with water and dried (anhydrous sodium sulphate). Removal of the solvent afforded an oil (430 mg) which was chromatographed over silica gel (15 g; each fraction of 15 ml was taken). Elution with pet.ether-benzene (4:1) gave the oxime tosylate (CLXXVII) recrystallized from pet.ether-ether (420 mg), m.p. 170°; ν max 1600 cm^{-1} (C=C, aromatic); δ 8.15 and 7.5 integrating for 4 protons (typical of p-disubstituted benzene with J value of 9 Hz), 7.48 (4H, ascribable to protons of ring A of the steroid), 2.35s (3H, CH_3 group attached to benzene ring of the tosylate part), 2.2m (2H, $C7-H_2$), 0.71s (3H, $C13-CH_3$), 0.88 and 0.96 (other methyl protons).

Analysis. Found: C, 74.12; H, 8.51; N, 2.41.

$C_{33}H_{45}NSO_2$ requires : C, 74.01; H, 8.41; N, 2.60%.

The oxime tosylate (CLXXVII)(400 mg) dissolved in pet.ether and was kept over a column of neutral alumina (25 g; each fraction of 15 ml was taken) for about 10 hours and then eluted. Elution with pet.ether-benzene (5:1) gave the lactam (CLXXIV) as solid material which was recrystallised from pet.ether (320 mg), m.p. 98°; M^+ 391 ($C_{26}H_{39}NO$); λ max 239 nm; ν max 3280, 3150(-NH), 1670 (CONH), 1645 and 1590 cm^{-1} (C=C of benzenoid ring system); δ 10.0s (1H, disappeared on addition of D_2O; CONH), 7.11br,s (4H, aromatic protons, C1-H, C2-H, C3-H and C4-H), 2.2m (2H, $C7-H_2$), 0.71s (3H, C13-CH_3), 0.91 and 0.88 (other methyl protons).

Analysis. Found: C, 81.01; H, 10.4; N, 4.20

$C_{26}H_{39}NO$ requires : C, 81.87; H, 10.21; N, 3.67%

Schmidt reaction of the ketone (CLXIII); 6-aza-A-homo-19-norcholesta-1,3,5(10)-trien-7-one (CLXXIV)

A mixture of 19-norcholesta-1,3,5(10)-trien-6-one (CLXIII) (0.4 gm), dry benzene (5 ml) and conc. sulphuric acid (2 ml) was heated to a temperature of 50-60° and sodium azide (100 g) was added slowly with stirring. The reaction mixture was kept at this temperature for 10 hours and the reaction mixture was poured onto crushed ice. The benzene layer was separated and the aqueous layer extracted several times with chloroform. After usual work up of the organic extracts, and removal of the solvent under reduced pressure it provided a semi solid material which was

chromatographed over silica gel (10 gm). Each fraction of 15 ml was collected. Elution with benzene-chloroform (4:1) yielded the lactam (CLXXXIV), recrystallized from pet.ether (230 mg), m.p. and m.m.p. 88°. The i.r. and t.l.c. were identical with the lactam (CLXXXIV) prepared using p-toluenesulphonyl chloride and pyridine.

Oxidation of the ketone (CLVI): 1-methyl-19-norcholesta-1,3,5(10)-trien-6-one oxime (CLXXXIX)

A mixture of the ketone (CLVI) (600 mg), hydroxylamine hydrochloride (1.4 g), sodium acetate trihydrate (1.6 g) and ethanol (50 ml) was heated under reflux for 2 hours. Most of the solvent was removed under reduced pressure and the residue thus obtained was recrystallized from pet.ether (500 mg), m.p. 135°; M^+ 395 ($C_{27}H_{41}NO$); λ max 255 nm; ν max 3230s (N-H), 3070w (C=C-H), and 1600 cm^{-1} (C=C, aromatic); δ 9.45br,s (1H, disappeared on addition of D_2O; N-OH), 7.35 m (1H, C8-H), 7.16s (2H, C2-H and C4-H), 2.13s (3H, C1-CH_3), 0.68s (C13-CH_3), 0.93 and 0.93 (other methyl signals).

Analysis. Found: C, 81.95; H, 10.54; N, 3.44

$C_{27}H_{41}NO$ requires : C, 82.02; H, 10.37; N, 3.53%.

Beckmann rearrangement of the oxime (CLXXIX); 1-methyl 13-nor-3-aza-4-homocholesta-1,3,5(10)-trien-7-one (CXC)

To a solution of the oxime (CLXXIX)(530 mg) in pyridine (12 ml; freshly distilled over KOH) was added p-toluenesulphonyl chloride (900 mg) and the reaction mixture was allowed to stand at room temperature for 15 hours. It was then poured into ice-cooled water and extracted with ether. The ethereal layer was washed with water, dilute sulphuric acid, sodium bicarbonate solution (5 %) and water and dried (anhydrous sodium sulphate). Removal of the solvent provided an oil (450 mg). The crude material in light pet.ether-benzene was allowed to stand over a column of neutral alumina (15 g) for about 15 hours. Each fraction of 15 ml was taken. Elution with pet.ether-chloroform (3:1) afforded the lactam (CCX), recrystallized from pet.ether-ether (400 mg), m.p. 170-71°; $[\alpha]_D$ 395 ($C_{27}H_{41}NO$); λ max 240 nm; ν max 3400, 3130 (NH), 3030 (C=C-H), 1670 (CONH), 1645 and 1585 cm^{-1} (C=C, aromatic); δ 10.15s (1H, disappeared on addition of D_2O; CONH), 6.95m (3H, C2-H, C3-H, C4-H, vinylic protons of ring A), 2.45s (3H, CH_3 attached to benzenoid ring A; C1-CH_3), 3.2m (3H, C7-H_2), 0.91, 0.85, 0.80 (other methyl protons).

Analysis. Found: C, 81.09; H, 10.16; N, 4.2

$C_{27}H_{41}NO$ requires: C, 82.02; H, 10.37; N, 3.37%.

Schmidt reaction of the ketone (CLVI); 1-methyl-19-nor-6-aza-D-homocholesta-1,3,5(10)-trien-7-one (CXC)

To a solution of 1-methyl-19-norcholesta-1,3,5(10)-trien-7-one (CLVI)(400 mg) in dry benzene (5 ml) and conc. sulphuric acid (1.0 ml), sodium azide (70 mg) was added with stirring at 55-60° on water bath. A brisk reaction ensued and after heating for 10 hours the reaction mixture was poured onto crushed ice. The benzene was separated and the aqueous layer extracted several times with chloroform. After usual work up of the organic extract, the solvent was removed under reduced pressure and the semi solid substance (300 mg) thus obtained was chromatographed over silica gel (15 g). Each fraction of 15 ml was taken. Elution with pet.ether-chloroform (2:1) provided a lactam (CXC), recrystallized from pet.ether-ether (160 mg), m.p. and m.m.p. 170-71°; its spectral values were identical with the lactam (CXC) obtained by subjecting the oxime (CLXXIX) to Beckmann rearrangement conditions.

The mass spectra were measured on an AEI-9 mass spectrometer at 70eV using a direct insertion technique at source temperature of about 200°C. The accurate mass measurement were relative to fragment ions of heptacosafluorotributyl amine at resolving power of 15,000.

The value (m/e) of the fragment ions from various compounds are tabulated below. The value in parentheses are the relative abundance (%) of the peaks with respect to base peak as 100%, and the composition of fragment ions as determined by accurate mass measurement.

Cholesta-2,4-dien-6-one (CXXXV)

M^+ 382 ($C_{27}H_{42}O$), m/e 367 (32.2), 366 (6.4), 364 (8.1), 349 (3.2), 339 (6.5; $C_{25}H_{38}$), 323 (3.2), 269 (4.8), 251 (8.1), 247 (19.3), 243 (4.8), 225 (33.8), 220 (11.3), 212 (12.9), 211 (25.8), 209 (11.3), 206 (8.1), 195 (8.1), 183 (12.9), 172 (22.5), 171 (16.1), 170 (11.3), 163 (12.9), 161 (8.1), 157 (36.2), 156 (29.29), 155 (25.8), 150 (17.7), 147 (8.1), 145 (12.9), 143 (11.3), 135 (59.6; $C_9H_{11}O$), 133 (17.7), 119 (49.9; C_8H_7O), 109 (32.2), 107 (41.9), 105 (100; C_7H_5O), 97 (24.2), 95 (49.9), 93 (46.6), 91 (69.2), 83 (32.2), 81 (48.37), 79 (30.6), 77 (29.0).

5α-Cholestan-3,6-dione (CLVII)

M^+ 400 (100; $C_{27}H_{44}O_2$), m/e 385 (33.07), 382 (4.7), 372 (9.4), 331 (4.7), 330 (6.3), 329 (6.3), 305 (6.3), 287 (61.3), 260 (15.7), 259 (6.3), 245 (31.6), 231 (28.3), 191 (12.6), 189 (11.0), 177 (11.0), 175 (17.3), 173 (9.4), 163 (11.0), 161 (14.1), 149 (25.1), 137 (48.4), 123 (34.5), 122 (40.8), 121 (34.5), 109 (56.5), 107 (55.0), 95 (66.0), 93 (58.1), 84 (75.4), 81 (91.6).

19-Norcholesta-1,3,5(10)-trien-6-one (CLXIII)

M^+ 366 ($C_{26}H_{38}O$)(82.0), m/e 351 (3.4), 253 (7.8), 227 (6.6), 226 (9.4), 225 (7.6), 212 (37.8), 211 (100; $C_{15}H_{15}O$), 198 (2.8), 197 (7.3), 184 (6.3), 183 (5.7), 171 (4.1), 170 (7.2), 169 (3.0), 159 (6.7), 158 (26.4), 157 (31.0), 156 (2.8), 145 (5.7), 144 (5.3), 141 (4.6), 131 (10.7), 129 (7.6), 128 (4.9), 115 (4.1), 103 (4.9),

1-Methyl-19-norcholesta-1,3,5(10)-trien-6-one (CLVI)

M^+ 380 (100; $C_{27}H_{40}O$), m/e 240 (14.1), 239 (13.7), 226 (47.4), 225 (90.6), 212 (41.0), 211 (91.4), 198 (16.9), 197 (13.2), 173 (11.7), 172 (69.1), 171 (59.9), 159 (20.5), 145 (27.2), 143 (12.5), 141 (10.3), 131 (12.7), 129 (17.8), 128 (13.0), 115 (15.0).

3 -Chlorocholest-5-en-7-one (CLXXIX)

M^+ 418/420 (100; $C_{27}H_{43}OCl$), 384 (17.85), 305/307 (42.8), 263/265 (21.42), 223/225 (37.7), 210/212 (96.39), 197/199 (32.13), 161 (49.98), 134 (46.41), 108 (32.13), 106 (21.42), 95 (10.71), 93 (32.13), 91 (39.27), 81 (35.7), 79 (28.56), 69 (17.85), 67 (24.99), 57 (35.7), 55 (29.56), 43 (65.26).

3 -Chloro-7a-aza-B-homocholest-5-en-7-one (CLXXXI)

M^+ 435/433 (19.04), m/e 420/418 (14.28), 400 (3.95), 398 (47.60), 397 (40.46), 396 (8.33), 390 (7.14), 383 (5.95), 382 (19.04), 370 (20.23), 367 (45.22), 354 (9.52), 320 (7.14), 284 (5.95), 264 (19.04), 263 (11.90), 262 (10.71), 248 (8.37), 247 (8.33), 222 (100; $C_9H_{15}N$), 223 (16.66), 212/210 (69.83), 199 (14.29), 176 (9.52), 175 (10.71), 174 (57.93), 173 (9.52), 171 (20.23), 151 (10.71), 150 (32.13), 138 (10.71), 137 (9.52), 136 (9.52), 135 (23.80), 134 (28.56), 133 (22.61), 132 (8.33), 131 (11.90), 120 (11.90), 110 (22.61), 109 (19.04), 108 (16.66), 107 (28.56), 105 (40.46), 95 (26.13), 94 (11.90), 93 (27.37), 91 (38.08), 83 (14.28), 82 (13.09), 81 (32.12), 79 (24.93), 72 (15.99), 70 (10.90).

19-Nor-6-aza-B-homocholesta-1,3,5(10)-trien-7-one (CLXXXIV)

m/e 383 (1.1), 382 (15.8), M^+ 381 (60.4; $C_{26}H_{39}NO$), 338 (6.9), 279 (10.9), 194 (6.4), 173 (4.2), 172 (5.9), 167 (33.3), 150 (10.9), 149 (100), 146 (12.4), 145 (4.2), 133 (5.4), 132 (7.1), 131 (4.1), 130 (17.0), 120 (15.6), 119 (21.1), 118 (4.2), 117 (5.4), 113 (15.6), 112 (9.3), 111 (4.5), 109 (3.7), 107 (4.9), 106 (11.3), 105 (7.8), 104 (5.3).

19-Norcholesta-1,3,5(10)-trien-6-one oxime (CLXXXVI)

M^+ 381 (100; $C_{26}H_{39}NO$), m/e 380 (3.69), 367 (3.15), 366 (17.88), 365 (58.91), 364 (24.19), 363 (3.15), 351 (3.15), 350 (9.46), 339 (4.20), 338 (8.41), 252 (6.31), 241 (10.52), 227 (9.99), 226 (27.35), 225 (8.41), 224 (13.67), 211 (13.67), 210 (34.1), 196 (9.46), 173 (14.70), 172 (3.67), 171 (3.67), 169 (7.87), 157 (16.80), 156 (8.92), 155 (13.65), 146 (6.30), 144 (7.35), 143 (7.87), 142 (8.40), 141 (28.35), 130 (9.45), 129 (6.30), 81 (6.92), 69 (8.40), 67 (6.30), 57 (10.5), 55 (15.93), 43 (37.75), 41 (12.60).

1-Methyl-19-nor-6-aza-B-homocholesta-1,3,5(10)-trien-7-one (CXC)

M^+ 395 (100; $C_{27}H_{41}NO$), m/e 380 (8.0), 367 (5.0), 353(21.6), 352 (34.49), 339 (7.2), 338 (7.2), 324 (3.60), 323 (4.32), 269 (4.32), 240 (5.14), 226 (5.14), 212 (5.76), 211 (6.48),

198 (7.2), 195 (7.2), 183 (8.64), 181 (6.48), 169 (12.24), 165 (9.0), 160 (6.48), 156 (7.2), 155 (17.28), 141 (30.24), 134 (18.72), 127 (11.52), 119 (14.40), 113 (15.84), 111 (20.16), 109 (12.96), 105 (14.40), 99 (20.16), 97 (31.68), 96 (10.08), 95 (18.72), 91 (11.52), 85 (6.48), 84 (4.89), 83 (3.98), 81 (2.01), 69 (7.2), 57 (7.77), 56 (4.99).

1-Methyl-19-norcholesta-1,3,5(10)-trien-6-one oxime (CLXXXIX)

M^+ 395 (7.94; $C_{27}H_{41}NO$), 394 (27.44), 380 (98.00), 379 (100; $C_{27}H_{41}N$), 378 (11.76), 377 (17.64), 348 (7.84), 324 (6.98), 322 (7.95), 294 (7.84), 250 (8.82), 254 (7.84), 251 (19.60), 130 (19.61), 129 (13.72), 128 (15.68), 116 (9.89), 115 (10.76), 107 (7.94), 95 (11.76), 83 (7.84), 81 (13.72), 79 (7.84), 70 (15.65), 68 (11.76), 57 (17.64), 55 (25.48), 43 (35.48).

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